World Health Organization

GUIDELINES



CONSOLIDATED GUIDELINES ON

HIV PREVENTION, TESTING, TREATMENT, SERVICE DELIVERY AND MONITORING:

RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH

JULY 2021

World Health Organization

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Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach

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FOREWORD

As we enter the third decade of widespread delivery of HIV services across the world, the global AIDS response continues to make steady progress in saving lives and reducing the number of people infected with HIV.

These consolidated guidelines on preventing and treating HIV infection bring together a series of recommendations to promote the highest quality, person-centred delivery of care for people living with and affected by HIV. The proposed tools and approaches correspond to the best available standard of care for low-and middle-income countries, as well as for high-income countries – erasing any differences in the standards of care based on where a person lives.

HIV still causes too many avoidable deaths, but by providing the right health services in a timely manner, we can avoid the worst consequences of the virus. The recommendations in these guidelines aim to reduce the number of people dying from HIV and, when fully implemented, will help us to reach our goals of reducing global HIV deaths to less than 200,000 by 2030.

For most people living with HIV, it is a chronic, lifelong condition. Evidence and lived experience have shown that with the right support, people are able to manage their own health according to what works best in their lives.

The service delivery approaches put forward in these guidelines aim to promote self-management for the majority of people living with or affected by HIV. This includes an expanded range of options for diagnosing, preventing, and treating HIV that are delivered and monitored in the community.

It is only by supporting people living with HIV, and the communities they belong to, that the world can hope to end AIDS as a public health threat.

I hope you will join me in promoting these important new guidelines and support WHO's efforts to help countries move towards ending AIDS by 2030.



Dr Tedros Adhanom Ghebreyesus
Director-General
World Health Organization



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ABBREVIATIONS AND ACRONYMS

1HP	daily isoniazid and rifapentine for one month
3HP	weekly isoniazid and rifapentine for three months
3TC	lamivudine
9H	daily isoniazid for nine months
Ab	antibody
Ag	antigen
ABC	abacavir
AIM	AIDS Impact Model
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral (drug)
ATV	atazanavir
AZT	zidovudine
BMI	body mass index
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CNS	central nervous system
d4T	stavudine
DAA	direct-acting antiviral (drug)
D:A:D	Data Collection on Adverse Events of Anti-HIV Drugs (study)
DALY	disability-adjusted life-year
DBS	dried blood spot (specimen)
ddI	didanosine
DHA	dihydroartemisinin
DMPA	depot medroxyprogesterone acetate
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz

ELISA	enzyme-linked immunosorbent assay
ETV	etravirine
FPV	fos-amprenavir
FTC	emtricitabine
GPRS	General Packet Radio Service
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GSM	Global System for Mobile Communications
HBV	hepatitis B virus
HCV	hepatitis C virus
HPV	human papillomavirus
HSV	herpes simplex virus
IATT	Interagency Task Team
IDV	indinavir
INSTI	integrase strand transfer inhibitor (also known as integrase inhibitor)
LA	latex agglutination
LAM	lipoarabinomannan
LF	urine lateral flow (test for diagnosing TB)
LGBQTI	lesbian, gay, bisexual, queer, transgender and intersex
LPV	lopinavir
LPV/r	lopinavir/ritonavir
mhGAP	WHO Mental Health Gap Action Programme
NAT	nucleic acid amplification testing
NFV	nelfinavir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
OR	odds ratio
PAHO	Pan American Health Organization
PCR	polymerase chain reaction
PEN	package of essential noncommunicable disease interventions
PEPFAR	United States President's Emergency Plan for AIDS Relief
PI	protease inhibitor
PICO	population, intervention, comparator, outcome

PEP	post-exposure prophylaxis
PrEP	pre-exposure prophylaxis
RAL	raltegravir
RR	relative risk
RT	reverse transcriptase
RTV	ritonavir
/r	low-dose ritonavir
SMS	short message service
SQV	saquinavir
TAF	tenofovir alafenamide
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TEE	tenofovir, emtricitabine and efavirenz
TLD	tenofovir, lamivudine and dolutegravir
TLE	tenofovir, lamivudine and efavirenz
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
VIA	visual inspection of the cervix with acetic acid

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EXECUTIVE SUMMARY

These guidelines provide guidance on the diagnosis of HIV infection, the care of people living with HIV and the use of antiretroviral (ARV) drugs for treating and preventing HIV infection. They are structured along the continuum of HIV testing, prevention, treatment and care. This edition updates the 2016 WHO consolidated guidelines, including updates and guidelines produced since.

The new UNAIDS 2025 targets place people living with HIV and communities at risk at the centre of the response and call for 95% of all people living with HIV knowing their HIV status, 95% who know their HIV-positive status initiating treatment and 95% of those receiving treatment having suppressed viral loads. They set clear targets for removing the societal and legal barriers to accessing services and emphasize the importance of integrating the HIV response with efforts to achieve universal health coverage as part of the Sustainable Development Goals.

Several significant developments have occurred in HIV since the last consolidated guidelines were published in 2016. These include the introduction of dolutegravir, self-testing, scaling up of viral load and infant testing and new options for tuberculosis (TB) preventive therapy and for post-exposure prophylaxis. Advanced HIV disease has been recognized as a persistent challenge to reducing mortality, and differentiated approaches to service delivery have demonstrated benefit in supporting the delivery of effective quality care. New point-of-care viral load testing technologies offer further potential to expand this approach.

In prevention, clinical trial results have strongly confirmed the efficacy of the ARV drug tenofovir disoproxil fumarate alone or in combination with emtricitabine for use as pre-exposure prophylaxis (PrEP) to prevent HIV transmission in a wide variety of settings and populations. WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection. For post-exposure prophylaxis, a two-drug regimen is effective, but a three-drug regimen of tenofovir disoproxil fumarate, lamivudine (or emtricitabine) and dolutegravir is preferred.

As countries continue to expand antiretroviral therapy (ART) coverage, ART initiation should follow the overarching principles of providing people-centred care. Rapid ART initiation should be offered to people living with HIV following a confirmed HIV diagnosis and clinical assessment, and ART initiation should be offered on the same day to people who are ready to start.

Implementing all the recommendations in these guidelines will have important implications for programme priority setting, funding and service delivery. As in 2016, service delivery guidance is included to help countries in implementing new approaches and strengthening the treatment cascade. Importantly, this guidance emphasizes the need for differentiated approaches to care for people who are established on ART, such as reducing the frequency of clinic visits and implementing community ART distribution. Such efficiencies are essential to reduce the burden on people receiving treatment and on health facilities. This guidance also provides recommendations for starting ART outside health facilities and tracing and reengagement in care.

These guidelines were revised in accordance with procedures established by the WHO Guideline Review Committee. Similar to the past, new clinical and operational recommendations in the guidelines are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to reviewing evidence; expert consultations and country case studies have all strongly informed these guidelines. The guideline development process has also identified key gaps in knowledge that will help to guide HIV research.

The primary audience for these guidelines is national HIV programme managers in low- and middle-income countries. The guidelines will also be a useful resource for clinicians and other health-care providers, especially those working in primary care services that are the first point of contact for recipients of care. The guidelines will also be of interest to national HIV treatment advisory boards, national HIV and TB programme managers, community- and faith-based organizations and international and bilateral agencies and organizations that provide technical and financial support to HIV programmes in resource-limited settings.

The guidelines will also be of value to people living with HIV, communities and civil society organizations, which will need to be engaged meaningfully to support their successful implementation.

COVID-19 has put the world even further behind its efforts to end the HIV epidemic as a public health threat by 2030. COVID-19 has affected services for HIV, viral hepatitis, sexually transmitted infections and harm reduction, with many countries reporting disruption in HIV services at the height of the pandemic. The full impact of COVID-19 will become apparent as additional clinical, epidemiological and psychosocial data become available.

The 2021 consolidated HIV guidelines represent an important step towards achieving universal access to ARV drugs for treating and preventing HIV – and the ultimate goal of ending the HIV epidemic as a major public health threat by 2030.

SUMMARY RECOMMENDATIONS

Summary of recommendations

The following table presents all recommendations and good practice statements included in these guidelines.

The ★ symbol represents recommendations or good practice statements developed between 2020 and 2021.

Chapter 2: HIV testing and diagnosis

2.4. HIV testing service delivery approaches

2.4.1 Facility-based HIV testing services

High-HIV-burden settings

HIV testing should be offered to all populations and in all services (for example, services for sexually transmitted infections, hepatitis, TB, children under five, immunization, malnutrition, antenatal care and all services for key populations) as an efficient and effective way to identify people with HIV.

Low-HIV-burden settings

HIV testing should be offered for:

- adults, adolescents or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including TB, viral hepatitis and sexually transmitted infections;
- HIV-exposed children and symptomatic infants and children;
- key populations and their partners; and
- all pregnant women.

2.4.2 Facility-based HIV testing services for infants and children

High-HIV-burden settings

In settings with a high burden of HIV infection, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV *(strong recommendation, low-certainty evidence).*

High-HIV-burden settings

In settings with a high burden of HIV infection, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics *(conditional recommendation, low-certainty evidence).*

Good practice statement

In all settings, the biological children of a parent living with HIV (or who may have died from HIV) should be routinely offered HIV testing services and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention and offered a broader package of voluntary provider-assisted referral.

2.4.3 Community-based HIV testing services

High-HIV-burden settings

Community-based HIV testing services are recommended, with linkage to prevention, treatment and care services, in addition to routine facility-based testing, for all populations, particularly key populations *(strong recommendation, low-certainty evidence).*

Chapter 2: HIV testing and diagnosis (continued)

High-HIV-burden settings

Community-based HIV testing services are recommended for key populations, with linkage to prevention, treatment and care services, in addition to routine facility-based testing *(strong recommendation, low-certainty evidence).*

2.4.4 HIV self-testing

HIV self-testing should be offered as an approach to HIV testing *(strong recommendation, moderate-certainty evidence).*

Remarks

- Providing HIV self-testing service delivery and support options is desirable.
- Communities need to be engaged in developing and adapting HIV self-testing models.
- HIV self-testing does not provide a definitive HIV-positive diagnosis. Individuals with a reactive test result must receive further testing from a trained tester using the national testing algorithm.

2.4.5 HIV partner services

Provider-assisted referral should be offered to people with HIV as part of a comprehensive package of testing and care *(strong recommendation, moderate-certainty evidence).*

Social network–based approaches can be offered as an HIV testing approach for key populations as part of a comprehensive package of care and prevention *(conditional recommendation, very-low-certainty evidence).*

Good practice statement

In all settings, biological children with a parent living with HIV (or who may have died from HIV) should be routinely offered HIV testing services and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention and offered a broader package of voluntary provider-assisted referral.

Note: Partner services include partner notification, contact tracing, index testing and family-based index case testing for reaching the partners of people living with HIV. These guidelines define partner services as encompassing a range of partner services packages and approaches, including social network–based approaches.

2.6.7 Priority populations

Infants and children

Addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis testing approaches can be considered to identify HIV infection among HIV-exposed infants *(conditional recommendation, low-certainty evidence).*

In settings with a high burden of HIV infection, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV *(strong recommendation, low-certainty evidence).*

In settings with a high burden of HIV infection, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics *(conditional recommendation, low-certainty evidence).*

Point-of-care nucleic acid testing should be used to diagnose HIV among infants and children younger than 18 months of age *(strong recommendation, high-certainty evidence).*

Rapid diagnostic tests for HIV serology can be used to assess HIV exposure among infants younger than four months of age. HIV-exposure status among infants and children 4–18 months of age should therefore be ascertained by HIV serological testing the mother *(conditional recommendation, low-certainty evidence).*

Rapid diagnostic tests for HIV serology can be used to diagnose HIV infection among children older than 18 months following the national testing strategy *(strong recommendation, moderate-certainty evidence).*

An indeterminate range of viral copy equivalents should be used to improve the accuracy of all nucleic acid–based early infant diagnosis assays *(strong recommendation, moderate-certainty evidence).*

Chapter 2: HIV testing and diagnosis (continued)

Good practice statements

National regulatory agencies are encouraged not to delay the adoption of point-of-care early infant diagnosis by conducting further evaluations but instead to adopt a rapid and streamlined registration and national approval process for immediate implementation.

In all settings, biological children with a parent living with HIV (or who may have died of HIV) should be routinely offered HIV testing services and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention and offered a broader package of voluntary provider-assisted referral.

Adolescents

HIV testing services, with linkages to prevention, treatment and care, are recommended for adolescents from key populations *(strong recommendation, very-low-certainty evidence).*

Adolescents should be counselled about the potential benefits and risks of disclosing their HIV-positive status and empowered and supported to determine whether, when, how and to whom to disclose *(conditional recommendation, very-low-certainty evidence).*

Settings with a high burden of HIV infection
In settings with a high burden of HIV infection, HIV testing services, with linkage to prevention, treatment and care, are recommended for all adolescents (strong recommendation, very-low-certainty evidence).

Settings with a low burden of HIV infection
HIV testing services, with linkage to prevention, treatment and care, should be accessible to adolescents in low and concentrated epidemics[a] *(conditional recommendation, very-low-certainty evidence).*

[a] Now referred to as settings with a low burden of HIV infection.

Good practice statement

Governments should revisit age-of-consent policies, considering the need to uphold adolescents' rights to make choices about their own health and well-being (with consideration for different levels of maturity and understanding).

Infants and children

HIV testing services should be routinely offered to all key populations both in the community and in facility-based settings. Community-based HIV testing, with linkage to prevention, treatment and care, should be offered, in addition to routinely offering testing in facilities, for key populations in all settings *(strong recommendation, low-certainty evidence).*

Social network–based approaches can be offered as an HIV testing approach for key populations as part of a comprehensive package of care and prevention *(conditional recommendation, very-low-certainty evidence).*

Pregnant women, couples and partners

All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)[a] at least once and as early as possible *(syphilis: strong recommendation, moderate-certainty evidence; HBsAg[a]: strong recommendation, low-certainty evidence).*

Dual HIV and syphilis rapid diagnostic tests can be the first test in HIV testing strategies and algorithms in antenatal care.

[a] Particularly in settings with a ≥2% HBsAg seroprevalence in the general population.

Provider-assisted referral should be offered to all people with HIV as part of a voluntary comprehensive package of testing and care *(strong recommendation, moderate-certainty evidence).*

Couples and partners should be offered voluntary HIV testing services with support for mutual disclosure *(strong recommendation, low-certainty evidence).*

Chapter 2: HIV testing and diagnosis (continued)

Women who disclose any form of violence by an intimate partner (or other family member) or sexual assault by any perpetrator should be offered immediate support. Health-care providers should, as a minimum, offer first-line support when women disclose violence. If health-care providers are unable to provide first-line support, they should ensure that someone else (within their health-care setting or another that is easily accessible) is immediately available to do so *(strong recommendation, indirect evidence).*

Health-care providers should ask about exposure to intimate partner violence when assessing conditions that may be caused or complicated by intimate partner violence, to improve diagnosis and identification and subsequent care *(strong recommendation, indirect evidence).*

Good practice statement

Mandatory or coercive testing is never warranted. In consultation with the client, the provider should assess the risk of harm, the most appropriate approach for couple and partner testing, including more supportive options such as provider assistance, and situations that make couple or partner testing inadvisable.

2.6. Strategies to make HIV testing services accessible

Task sharing

Lay providers who are trained and supervised to use rapid diagnostic tests can independently conduct safe and effective HIV testing services *(strong recommendation, moderate-certainty evidence).*

2.7. Maintaining the accuracy and reliability of HIV diagnosis

Western blotting

Western blotting and line immunoassays should not be used in national HIV testing strategies and algorithms *(strong recommendation, low-certainty evidence).*

HIV testing strategy and algorithm

WHO recommends that all HIV testing algorithms achieve at least 99% positive predictive value and use a combination of tests with ≥99% sensitivity and ≥98% specificity.

The first test in an HIV testing strategy and algorithm should have the highest sensitivity, followed by a second and third test of the highest specificity.

Countries should consider moving to a three-test strategy as HIV positivity within national HIV testing service programmes falls below 5% – meaning all people presenting for HIV testing services should have three consecutive reactive test results in order to receive an HIV-positive diagnosis.

Dual HIV/syphilis rapid diagnostic tests can be the first test in HIV testing strategies and algorithms in antenatal care.

WHO suggests using a testing strategy for HIV diagnosis that is suitable for HIV diagnosis during surveillance and routinely returning HIV test results to participants.

Chapter 2: HIV testing and diagnosis (continued)

Retesting prior to ART initiation

All people newly diagnosed with HIV should be retested to verify their HIV status prior to starting ART, using the same testing strategy and algorithm as the original diagnosis.

Retesting among people with HIV who already know their status, including those on treatment, is not recommended as it can provide incorrect results if the person with HIV is on ART.

2.8. HIV diagnosis among infants and children

2.8.1 Timing of virological testing

The addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis testing approaches can be considered to identify HIV infection in HIV-exposed infants *(conditional recommendation, low-certainty evidence).*

2.8.3 Technologies to use for infant testing



Point-of-care nucleic acid testing should be used to diagnose HIV among infants and children younger than 18 months of age *(strong recommendation, high-certainty evidence).*

2.8.4 Rapid diagnostic tests for HIV serology

Rapid diagnostic tests for HIV serology can be used to assess HIV exposure among infants younger than four months of age. HIV-exposure status among infants and children four to 18 months of age should therefore be ascertained by undertaking HIV serological testing in the mother *(conditional recommendation, low-certainty evidence).*

Rapid diagnostic tests for HIV serology can be used to diagnose HIV infection among children older than 18 months following the national testing strategy *(strong recommendation, moderate-certainty evidence).*

2.8.5 Minimizing false-positive results by introducing an indeterminate range for infant diagnosis when using NAT

An indeterminate range[a] of viral copy equivalents should be used to improve the accuracy of all nucleic acid–based early infant diagnosis assays *(strong recommendation, moderate-certainty evidence).*

[a] Indeterminate range: a range of viral copy equivalents that would be too low to be accurately diagnosed as HIV infected. The indeterminate range suggested is currently estimated to be approximately equivalent to a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay.

Chapter 3: HIV prevention

3.2 Pre-exposure prophylaxis for preventing the acquisition of HIV

3.2.1 Oral pre-exposure prophylaxis for preventing the acquisition of HIV

Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection[a] as part of combination HIV prevention approaches *(strong recommendation, high-certainty evidence).*

[a] See Box 3.2 for reflections on the definition of substantial risk of HIV infection.

3.2.2 PrEP using the dapivirine vaginal ring

The dapivirine vaginal ring may be offered as an additional prevention choice for women[a] at substantial risk of HIV infection as part of combination prevention approaches *(conditional recommendation, moderate-certainty evidence).*

[a] For the recommendation on the dapivirine vaginal ring, the term women applies to cisgender women, meaning women assigned female at birth. There is no research at this time to support the dapivirine vaginal ring for other populations.

3.3 Post-exposure prophylaxis

Overall

An HIV post-exposure prophylaxis (PEP) regimen with two ARV drugs is effective, but three drugs are preferred *(conditional recommendation, low-certainty evidence).*

Adults and adolescents

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV PEP *(strong recommendation, low-certainty evidence).*

DTG is recommended as the preferred third drug for HIV PEP *(strong recommendation, low-certainty evidence).*

When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for PEP *(conditional recommendation, low-certainty evidence).*

Children*

AZT + 3TC is recommended as the preferred backbone regimen for HIV PEP for children 10 years and younger. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens *(strong recommendation, low-certainty evidence).*

DTG is recommended as the preferred third drug for HIV PEP with approved DTG dosing *(strong recommendation, low-certainty evidence).*

When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for PEP *(conditional recommendation, low-certainty evidence).*

* The choice of ARV drugs for children will depend on the availability of approved dosing and age-appropriate formulations for children.

Chapter 3: HIV prevention (continued)

3.4 Infant prophylaxis

Good practice statement

ART should be initiated urgently among all pregnant and breastfeeding women living with HIV, even if they are identified late in pregnancy or postpartum, because the most effective way to prevent HIV vertical transmission is to reduce maternal viral load.[a]

[a] Whenever possible, all efforts should be made to identify HIV-infected pregnant women early enough to avoid the need for enhanced prophylaxis.

Infants born to mothers with HIV who are at high risk of acquiring HIVb should receive dual prophylaxis with daily AZT and NVP for the first six weeks of life, whether they are breastfed or formula fed *(strong recommendation, moderate-certainty evidence).*

Breastfed infants who are at high risk of acquiring HIV[b], including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional six weeks (total of 12 weeks of infant prophylaxis) using either AZT and NVP or NVP alone *(conditional recommendation, low-certainty evidence).*

[b] High-risk infants are defined as those:

- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; or
- born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load is available; or
- born to women with incident HIV infection during pregnancy or breastfeeding; or
- born to women identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT) *(strong recommendation, moderate-certainty evidence for breastfeeding infants; strong recommendation, low-certainty evidence for infants receiving only replacement feeding).*

Chapter 4: ART for people living with HIV

4.4 When to start ART

All populations

ART should be initiated for all people living with HIV regardless of WHO clinical stage and at any CD4 cell count.

- Adults *(strong recommendation, moderate-certainty evidence)*
- Pregnant and breastfeeding women *(strong recommendation, moderate-certainty evidence)*
- Adolescents *(conditional recommendation, low-certainty evidence)*
- Children living with HIV one year old to less than 10 years old *(conditional recommendation, low-certainty evidence)*
- Infants diagnosed in the first year of life *(strong recommendation, moderate-certainty evidence)*

4.5 Timing of ART

4.5.1 Rapid ART initiation

Rapid ART initiation[a] should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment (strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).

[a] Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start *(strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).*

Good practice statement

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and should promote engaging and supporting people and families to play an active role in their own care by informed decision-making. People should be encouraged but not coerced to start ART immediately and should be supported in making an informed choice regarding when to start ART and what ARV drug regimen to use.

4.5.2 Timing of ART for adults, adolescents and children being treated for HIV-associated TB

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a]

Adults and adolescents *(strong recommendation, low- to moderate-certainty evidence)*

Children and infants *(strong recommendation, very-low-certainty evidence)*

[a] Except when signs and symptoms of meningitis are present.

4.5.3 Timing of ART for people living with HIV and cryptococcal meningitis

Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment *(strong recommendation, low-certainty evidence for adults and very-low-certainty evidence for children and adolescents).*

4.5.4 Timing of ART for people living with HIV and histoplasmosis

ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven *(conditional recommendation, very-low-certainty evidence).*

Chapter 4: ART for people living with HIV (continued)

4.6 What to start

4.6.1 First-line ART

Preferred regimen

1. DTG in combination with an NRTI backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART.[a]

- Adults and adolescents *(strong recommendation, moderate-certainty evidence)*
- Infants and children with approved DTG dosing[b] *(conditional recommendation, low-certainty evidence)*

[a] In settings or populations in which DTG is not accessible or unsuitable because of toxicity and national levels of pretreatment HIV drug resistance are ≥10%, PI/r-based ARV drugs should be used in first-line ART. The choice of PI/r will depend on the programmatic characteristics. Alternatively, and if feasible, HIV drug resistance testing can be considered to guide the selection of first-line ART regimen (see Section 4.9 and Table 4.3).

[b] As of July 2021, the United States Food and Drug Administration and the European Medicines Agency have approved DTG for infants and children older than four weeks and weighing at least 3 kg.

Alternative regimen (adults and adolescents)

2. EFV at low dose (400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART[a] *(strong recommendation, moderate-certainty evidence)*.

[a] In settings in which pretreatment HIV drug resistance to NNRTIs is ≥10%, EFV-based ART should be avoided. EFV should also be avoided for people initiating or reinitiating first-line regimens with previous ARV drug exposure, regardless of the national prevalence of pretreatment drug resistance. See section 4.9 on HIV drug resistance considerations, Table 4.3 and Fig. 4.3.

Preferred regimen (neonates)

3. An RAL-based regimen may be recommended as the preferred first-line regimen for neonates *(conditional recommendation, very-low-certainty evidence).*

4.6.2 Second-line ART

Non-DTG-based regimens

DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.

- Adults and adolescents *(conditional recommendation, moderate-certainty evidence)*
- Children with approved DTG dosing *(conditional recommendation, low-certainty evidence)*

DTG-based regimens

Boosted protease inhibitors in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone are recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing *(strong recommendation, moderate-certainty evidence).*

4.6.3 Third-line ART

National programmes should develop policies for third-line ART *(conditional recommendation, low-certainty evidence).*

Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs *(conditional recommendation, low-certainty evidence).*

People receiving a failing second-line regimen with no new ARV drug options should continue with a tolerated regimen *(conditional recommendation, very low-certainty evidence).*

Chapter 4: ART for people living with HIV (continued)

4.7 Monitoring the response to ART

Preferred monitoring approach

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure[a] *(strong recommendation, low-certainty evidence).*

[a] Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended in settings in which logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

Point-of-care viral load testing may be used to monitor treatment among people living with HIV receiving ART[b] *(conditional recommendation, moderate-certainty evidence).*

[b] See section 4.7 on using point-of-care viral load testing.

Timing of treatment monitoring

Routine viral load monitoring can be carried out by six months, at 12 months and then every 12 months thereafter if the person is established on ART to synchronize with routine monitoring and evaluation reporting *(conditional recommendation, very-low-certainty evidence).*

See Fig. 4.2 for an updated treatment monitoring algorithm.

Role of CD4 cell count monitoring

In settings in which routine viral load monitoring is available, CD4 cell count[a] monitoring can be stopped for individuals who are established on ART[b] *(conditional recommendation, low-certainty evidence).*

[a] The timing and use of CD4 remains the same as in the 2016 WHO consolidated guidelines.

[b] Being established on ART includes suppressed viral loads (see section 7.3).

In settings where viral load is not routinely available

If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure *(strong recommendation, moderate-certainty evidence).*

Use of dried blood spot specimens

Dried blood spot specimens using venous or capillary whole blood can be used to determine HIV viral load. A threshold of 1000 copies/mL can be used to determine virological failure when using dried blood spot samples, as defined for testing in plasma[a] *(conditional recommendation, low-certainty evidence).*

[a] Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended in settings in which logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

4.9 ARV drug resistance

For people initiating first-line ART with pretreatment HIV drug resistance to NNRTIs, a NNRTI-containing regimen should be avoided *(conditional recommendation, low-certainty evidence).*

Consensus statement

In countries in which the prevalence of pretreatment HIV drug resistance to NNRTIs among people initiating first-line ART is equal to or greater than 10%, NNRTI-based ART should be avoided.

Chapter 5: Advanced HIV disease

5.3 Providing a package of care

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease *(strong recommendation, moderate-certainty evidence).*

5.4 Overview of clinical management of cryptococcal disease

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease *(strong recommendation, moderate-certainty evidence).*

Diagnosis of cryptococcal meningitis

For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of CSF opening pressure and rapid cryptococcal antigen assay is recommended as the preferred diagnostic approach *(strong recommendation, moderate-certainty evidence for adults and adolescents).*

The following diagnostic approaches are recommended, according to the context:

Settings with ready access to and no contraindication for lumbar puncture

1. If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available: lumbar puncture with rapid CSF cryptococcal antigen assay is the preferred diagnostic approach *(strong recommendation, moderate-certainty evidence for adults and adolescents).*

2. If access to a cryptococcal antigen assay is not available and/or rapid results are not available: lumbar puncture with CSF India ink test examination is the preferred diagnostic approach *(strong recommendation, moderate-certainty evidence for adults and adolescents).*

Settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated such as significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs or recurrent seizures

1. If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available: rapid serum, plasma or whole-blood cryptococcal antigen assays are the preferred diagnostic approaches *(strong recommendation, moderate-certainty evidence for adults and adolescents).*

2. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured: prompt referral for further investigation and treatment as appropriate *(strong recommendation, moderate-certainty evidence for adults and adolescents).*

Prevention and screening

Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease are recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3 *(strong recommendation, moderate-certainty evidence).*

This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(conditional recommendation, moderate-certainty evidence).*

Chapter 5: Advanced HIV disease (continued)

All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis and undergo a lumbar puncture, if feasible, with CSF examination and India ink or CSF cryptococcal antigen assay to exclude active cryptococcal disease. India ink has low sensitivity, and a negative result on India ink should be confirmed by CSF cryptococcal antigen testing. When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3 *(strong recommendation, moderate-certainty evidence).*
This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(conditional recommendation, moderate-certainty evidence).*

Treatment

The following is recommended as the preferred induction regimen.
For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) is the preferred option for treating cryptococcal meningitis among people living with HIV *(strong recommendation, moderate-certainty evidence for adults).*

The following induction regimens are recommended as alternative options.

- Two weeks of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) + flucytosine (100 mg/kg per day, divided into four doses per day) *(strong recommendation, moderate-certainty evidence).*
- Two weeks of amphotericin B deoxycholate (1.0 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) *(strong recommendation, moderate-certainty evidence).*

Consolidation
Fluconazole (400–800 mg daily for adults or 6–12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase (for eight weeks following the induction phase) *(strong recommendation, low-certainty evidence).*

Maintenance (or secondary prophylaxis)
Fluconazole (200 mg daily for adults or 6 mg/kg per day for adolescents and children) is recommended for the maintenance phase *(strong recommendation, high-certainty evidence).*

Using adjunctive systemic corticosteroids in treating cryptococcal meningitis

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating adults, adolescents and children who have HIV-associated cryptococcal meningitis *(strong recommendation, high-certainty evidence for adults and adolescents).*

Timing of ART

Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4–6 weeks from the initiation of antifungal treatment *(strong recommendation, low-certainty evidence for adults).*

Chapter 5: Advanced HIV disease (continued)

5.5 Overview of clinical management of histoplasmosis

Diagnosis of disseminated histoplasmosis among people living with HIV

Among people living with HIV, disseminated histoplasmosis should be diagnosed by detecting circulating Histoplasma antigens *(conditional recommendation, low-certainty evidence).*

Induction therapy

Treating people living with HIV for severe or moderately severe histoplasmosis: liposomal amphotericin B, 3.0 mg/kg, for two weeks is recommended. In settings in which liposomal amphotericin B is unavailable, deoxycholate amphotericin B, 0.7–1.0 mg/kg, is recommended for two weeks *(conditional recommendation, very-low-certainty evidence).*

Good practice statements

As a good practice for people with renal failure, or at risk of renal injury, measures to prevent or treat toxicity are recommended.

Induction therapy should be given for two weeks. Since deoxycholate amphotericin B may be associated with renal toxicity, therapy may need to be shorter than two weeks based on the clinical assessment of how the person responds to treatment. Involvement of the central nervous system may require extending induction therapy or increasing dosage.

Treating people living with HIV for mild to moderate histoplasmosis: itraconazole 200 mg three times daily for three days and then 200 mg twice daily is recommended *(conditional recommendation, very-low-certainty evidence).*

Maintenance therapy

Itraconazole 200 mg twice daily for 12 months is recommended *(conditional recommendation, very-low-certainty evidence).*

Less than 12 months of therapy can be considered when the person is clinically stable, receiving ART, has suppressed viral load and the immune status has improved *(conditional recommendation, very-low-certainty evidence).*

Timing of ART

ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven *(conditional recommendation, very-low-certainty evidence).*

TB therapy for people coinfected with TB, HIV and histoplasmosis

People living with HIV who also have TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines *(conditional recommendation, very-low-certainty evidence).*

Chapter 6: Coinfections and comorbidities

6.2. General care for people living with HIV

Children and adolescents

Children and adolescents should do at least an average of 60 minutes per day of moderate- to vigorous-intensity, mostly aerobic, physical activity, across the week *(strong recommendation, moderate-certainty evidence).*

Vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone, should be incorporated at least three days a week *(strong recommendation, moderate-certainty evidence).*

Children and adolescents should limit the amount of time spent being sedentary, particularly the amount of recreational screen time *(strong recommendation, low-certainty evidence).*

Adults (18–64 years old) and older adults (65 years and older), including those with chronic conditions

All adults should undertake regular physical activity *(strong recommendation, moderate-certainty evidence).*

Adults should do at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits *(strong recommendation, moderate-certainty evidence).*

Adults should also do muscle strengthening activities at moderate or greater intensity that involve all major muscle groups on two or more days a week, since these provide additional health benefits *(strong recommendation, moderate-certainty evidence).*

Adults may increase moderate-intensity aerobic physical activity to more than 300 minutes; or do more than 150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for additional health benefits *(conditional recommendation, moderate-certainty evidence).*

Adults should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits *(strong recommendation, moderate-certainty evidence).*

To help reduce the detrimental effects of high levels of sedentary behaviour on health, adults should aim to do more than the recommended levels of moderate- to vigorous-intensity physical activity *(strong recommendation, moderate-certainty evidence).*

Additional recommendation for older adults (65 years and older)

As part of their weekly physical activity, older adults should do varied multicomponent physical activity that emphasizes functional balance and strength training at moderate or greater intensity, on three or more days a week, to enhance functional capacity and to prevent falls *(strong recommendation, moderate-certainty evidence).*

6.3. Co-trimoxazole prophylaxis

Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with CD4 cell count ≤350 cells/mm^3 *(strong recommendation, moderate-certainty evidence).*

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage *(conditional recommendation, moderate-certainty evidence).*

Co-trimoxazole prophylaxis may be discontinued for adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression *(conditional recommendation, low-certainty evidence).*

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage *(conditional recommendation, moderate-certainty evidence).*

Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 cell count ≤350 cells/mm^3 *(strong recommendation, high-certainty evidence).*

Chapter 6: Coinfections and comorbidities (continued)

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood whether or not ART is being taken *(conditional recommendation, moderate-certainty evidence).*

In settings of low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children five years of age and older who are clinically stable and/or virally suppressed on ART for at least six months and CD4 cell count >350 cells/mm^3 *(strong recommendation, very-low-certainty evidence).*

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from four to six weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding *(strong recommendation, very-low-certainty evidence).*

Routine co-trimoxazole prophylaxis should be given to all people living with HIV with active TB disease regardless of CD4 cell count *(strong recommendation, high-certainty evidence).*

6.4. Tuberculosis

6.4.1 Screening and diagnosis

Systematic screening for TB among people living with HIV ★

People living with HIV should be systematically screened for TB disease at each visit to a health facility *(strong recommendation, very-low-certainty evidence).*

Tools for screening for TB among people living with HIV ★

Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four-symptom screen, and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases *(strong recommendation, moderate-certainty evidence).*

Among children younger than 10 years who are living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of the symptoms of current cough, fever, poor weight gain or close contact with a person with TB disease *(strong recommendations, low-certainty evidence for test accuracy).*

Among adults and adolescents living with HIV, C-reactive protein with a cut-off of >5 mg/L may be used to screen for TB disease *(conditional recommendation, low-certainty evidence for test accuracy).*

Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease *(conditional recommendation, moderate-certainty evidence for test accuracy).*

Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease *(conditional recommendation, low-certainty evidence).*

Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease *(conditional recommendation, moderate-certainty evidence for test accuracy).*

Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is >10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test *(strong recommendation, moderate-certainty evidence for test accuracy).*

6.4.3 Treatment

Treatment of people with drug-resistant TB ★

WHO recommends ART for all people with HIV and drug-resistant TB, requiring second-line anti-TB drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of anti-TB treatment *(strong recommendation, very-low-certainty evidence).*

Chapter 6: Coinfections and comorbidities (continued)

Identifying populations for latent TB infection testing and TB preventive treatment

Adults and adolescents

Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those receiving ART, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if latent TB infection testing is unavailable *(strong recommendation, high-certainty evidence).*

Infants aged <12 months

Infants aged <12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment *(strong recommendation, moderate-certainty evidence)*

Children aged ≥12 months

Children aged ≥12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with a person with TB *(strong recommendation, low-certainty evidence).*

All children

All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment *(conditional recommendation, low-certainty evidence).*

Algorithms to rule out active TB disease

Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status *(strong recommendation, moderate-certainty evidence).*

Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded *(strong recommendation, moderate-certainty evidence).*

Chest radiography may be offered to people living with HIV receiving ART and TB preventive treatment given to those with no abnormal radiographic findings *(conditional recommendation, low-certainty evidence).*

Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age *(strong recommendation, low-certainty evidence).*

The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥5 years and other risk groups before TB preventive treatment *(conditional recommendation, very-low-certainty evidence).*

Testing for latent TB infection

Either a tuberculin skin test or interferon-gamma release assay can be used to test for latent TB infection *(strong recommendation, very-low-certainty evidence).*

TB preventive treatment options

The following options are recommended for the treatment of latent TB infection regardless of HIV status: six or nine months of daily isoniazid, or a three-month regimen of weekly rifapentine plus isoniazid, or a three-month regimen of daily isoniazid plus rifampicin *(strong recommendation, moderate- to high-certainty evidence in the estimates of effect).*

Chapter 6: Coinfections and comorbidities (continued)

A one-month regimen of daily rifapentine plus isoniazid or four months of daily rifampicin alone may also be offered as alternatives *(conditional recommendation, low- to moderate-certainty evidence).*

In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive latent TB infection test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy. Daily isoniazid preventive therapy for 36 months should be given whether or not the person is receiving ART and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have high TB transmission as defined by national authorities *(conditional recommendation, low-certainty evidence).*

6.5. Hepatitis B and C

6.5.2 Testing for chronic HBV infection

General population testing

In settings with a ≥2% or ≥5%[a] HBsAg seroprevalence in the general population, it is recommended that all adults and adolescents have routine access to and be offered HBsAg serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or health facility–based testing opportunities or programmes such as at antenatal clinics, HIV or TB clinics *(conditional recommendation, low-certainty evidence).*

Routine testing in pregnant women

In settings with a ≥2% or ≥5%%[a] HBsAg seroprevalence in the general population, it is recommended that HBsAg serological testing be routinely offered to all pregnant women in antenatal clinics,[b] with linkage to prevention, care and treatment services. Couples and partners in antenatal care settings should be offered HBV testing services *(strong recommendation, low-certainty evidence).*

[a] A threshold of ≥2% or ≥5% seroprevalence was based on several published thresholds of intermediate or high seroprevalence. The threshold used will depend on other country considerations and the epidemiological context.

[b] Many countries have chosen to adopt routine testing in all pregnant women, regardless of seroprevalence in the general population, and especially if the seroprevalence ≥2%. A full vaccination schedule including birth dose should be completed for all infants, in accordance with the WHO position paper on HBV vaccines.

Focused testing in most affected populations

In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that HBsAg serological testing and linkage to care and treatment services be offered to the following individuals:

- adults and adolescents from populations most affected by HBV infection[c] (who either are part of a population with high HBV seroprevalence or have a history of exposure and/or high-risk behaviour for HBV infection);
- adults, adolescents and children for whom chronic viral hepatitis[d] is clinically suspected (through symptoms, signs or laboratory markers);
- sexual partners, children and other family members and close household contacts of those with HBV infection;[e] and
- health-care workers: in all settings, it is recommended that HBsAg serological testing be offered and HBV vaccination given to all health-care workers who have not been vaccinated previously (adapted from existing guidance on HBV vaccination) *(strong recommendation, low-certainty evidence).*

[c] Includes those who are either part of a population with higher seroprevalence (such as some mobile or migrant populations from high- or intermediate-endemic countries and certain indigenous populations) or have a history of exposure to or high-risk behaviour for HBV infection (such as people who inject drugs; people in prisons and other closed settings; gay men and other men who have sex with men; sex workers; people living with HIV; and partners, family members and children of people with HBV infection).

[d] Features that may indicate underlying chronic HBV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma, or unexplained liver disease, including abnormal liver function tests or liver ultrasound.

[e] In all settings, it is recommended that HBsAg serological testing with HBV vaccination of those who are HBsAg negative and not previously vaccinated be offered to all children with parents or siblings diagnosed with HBV infection or with clinical suspicion of hepatitis, through community- or facility-based testing.

Chapter 6: Coinfections and comorbidities (continued)

Blood donors

In all settings, screening of blood donors should be mandatory with linkage to care, counselling and treatment for those who test positive.

6.5.2 Testing for chronic HCV infection

Focused testing in most affected populations

In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that serological testing for HCV antibody[a] be offered with linkage to prevention, care and treatment services to the following individuals:

- adults and adolescents from populations most affected by HCV infection[b] (who are either part of a population with high HCV seroprevalence or have a history of exposure to and/or high-risk behaviour for HCV infection); and
- adults, adolescents and children for whom chronic viral hepatitis is clinically suspected[c] (through symptoms, signs or laboratory markers) *(strong recommendation, low-certainty evidence).*

[a] This may include fourth-generation combined antibody or antigen assays.

[b] Includes those who are either part of a population with higher seroprevalence (such as some mobile or migrant populations from high- or intermediate-endemic countries and certain indigenous populations) or have a history of exposure to or high-risk behaviour for HCV infection (such as people who inject drugs; people in prisons and other closed settings; gay men and other men who have sex with men; sex workers; people living with HIV; and the children of mothers with chronic HCV infection, especially if HIV-coinfected).

[c] Features that may indicate underlying chronic HCV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma or unexplained liver disease, including abnormal liver function tests or liver ultrasound.

General population testing

In settings with a ≥2% or ≥5%[d] HCV antibody seroprevalence in the general population, it is recommended that all adults have access to and be offered HCV serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or facility-based testing opportunities or programmes such as HIV or TB clinics, drug treatment services and antenatal clinics[e] *(conditional recommendation, low-certainty evidence).*

[d] Features that may indicate underlying chronic HCV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma or unexplained liver disease, including abnormal liver function tests or liver ultrasound.

[e] Routine testing of pregnant women for HCV infection is currently not recommended.

Birth cohort testing

This approach may be applied to specific identified birth cohorts of older people at higher risk of infection[f] and morbidity within populations that have an overall lower general prevalence *(conditional recommendation, low-certainty evidence).*

[f] Because of historical exposure to unscreened or inadequately screened blood products and/or poor injection safety.

6.5.5 Preventing mother-to-child transmission of HBV infection

Routinely testing pregnant women for HIV, HBV and syphilis

All pregnant women should be tested for HIV, syphilis and HBsAg at least once and as early as possible in the pregnancy *(HIV standing recommendation since 2007; syphilis: strong recommendation, moderate-certainty evidence; HBsAg: strong recommendation, low-certainty evidence).*

Immunization

All infants should receive their first dose of HBV vaccine as soon as possible after birth, preferably within 24 hours. Delivery of HBV vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose. The birth dose should be followed by two or three doses to complete the primary series.

Chapter 6: Coinfections and comorbidities (continued)

Tenofovir prophylaxis

Women coinfected with HIV and HBV should be receiving TDF-based ART, which will provide prophylaxis to prevent the mother-to-child transmission of HBV. This is in addition to three-dose HBV vaccination for all infants, including timely birth dose *(conditional recommendation, moderate-certainty evidence).*

6.6. Malaria

Good practice statement

For people who have HIV and uncomplicated *Plasmodium falciparum* malaria, avoid artesunate + sulfadoxine-pyrimethamine if they are being treated with co-trimoxazole and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

6.8. Leishmaniasis

People coinfected with visceral leishmaniasis and HIV in eastern Africa

Liposomal amphotericin B + miltefosine regimen
Liposomal amphotericin B (up to a total of 30 mg/kg at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for 28 days) *(conditional recommendation, very-low-certainty evidence)*

People coinfected with visceral leishmaniasis and HIV in South-East Asia

Liposomal amphotericin B + miltefosine regimen
Liposomal amphotericin B (up to a total of 30 mg/kg at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for 14 days) *(conditional recommendation, very-low-certainty evidence).*

Provide secondary prophylaxis after the first episode of visceral leishmaniasis for all people coinfected with visceral leishmaniasis and HIV *(conditional recommendation, very-low-certainty evidence).*

6.9. Cervical cancer

Screening and treatment recommendations to prevent cervical cancer for women living with HIV

WHO recommends using HPV DNA detection as the primary screening test rather than visual inspection of the cervix with acetic acid (VIA) or cytology in screening and treatment approaches among women living with HIV *(strong recommendation, moderate-certainty evidence).*

Remarks: Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.

WHO suggests using an HPV DNA primary screening test with triage rather than without triage to prevent cervical cancer among women living with HIV *(conditional recommendation, moderate-certainty evidence).*

In a screen, triage and treat approach using HPV DNA detection as the primary screening test, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women living with HIV after a positive HPV DNA test *(conditional recommendation, moderate-certainty evidence).*

Remarks: The benefits, harm and programmatic costs of the triage options are similar; therefore, the choice of triage method will depend on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test.

When HPV DNA testing is provided, WHO suggests using either samples taken by a health-care provider or self-collected samples *(conditional recommendation, low-certainty evidence).*

WHO suggests starting regular cervical cancer screening at the age of 25 years among women living with HIV *(conditional recommendation, low-certainty evidence).*

Remarks: Moderate-certainty evidence found that few women living with HIV younger than 25 years are likely to have cervical cancer. This recommendation applies to women living with HIV regardless of when they first tested positive for HIV.

Chapter 6: Coinfections and comorbidities (continued)

After the age of 50 years, WHO suggests that screening be stopped after two consecutive negative screening results, consistent with the recommended regular screening intervals among women living with HIV *(conditional recommendation, very-low-certainty evidence).*

Remarks: VIA and ablation treatment are not suitable for screening women for whom the transformation zone is not visible. Inadequate visualization is typical after menopause.

Good-practice statement

Priority should be given to screening women living with HIV 25–49 years old. When tools are available to manage postmenopausal women, women living with HIV 50–65 years old who have never been screened should also be given priority.

WHO suggests a regular screening interval of every 3–5 years when using HPV DNA detection as the primary screening test among women living with HIV *(conditional recommendation, low-certainty evidence).*

Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every three years when using VIA or cytology as the primary screening test among women living with HIV *(conditional recommendation, low-certainty evidence).*

Good-practice statement

While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial.

WHO suggests that women living with HIV who have screened positive on an HPV DNA primary screening test and then negative on a triage test be retested with HPV DNA testing in 12 months and, if negative, move to the recommended screening interval *(conditional recommendation, low-certainty evidence).*

WHO suggests that women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy be retested with HPV DNA testing in 12 months and, if negative, move to the recommended regular screening interval *(conditional recommendation, low-certainty evidence).*

WHO suggests that women living with HIV who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ or treated as a result of a positive screening test be retested in 12 months with HPV DNA testing when available rather than with cytology or VIA or co-testing, and, if negative, be retested again at 12 months and, if negative again, move to the recommended screening interval *(conditional recommendation, low-certainty evidence).*

Good-practice statement

As programmes introduce HPV DNA testing, use this test when rescreening women living with HIV regardless of the test that was used at the previous screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational.

General population and women living with HIV

Good practice statement

Once a decision to treat a woman is made, treating as soon as possible within six months is good practice to reduce losses to treatment. However, for women who are pregnant, good practice includes deferral until after pregnancy.

In circumstances when treatment is not provided within this time frame, evaluating the woman before treatment is good practice.

WHO suggests large loop excision of the transformation zone or cold-knife conization for women who have histologically confirmed adenocarcinoma in situ *(conditional recommendation, low-certainty evidence for effects).*

Remarks: Loop excision may be preferred for women of reproductive age, in settings with greater availability of large loop excision of the transformation zone and by providers with greater expertise performing large loop excision of the transformation zone. Cold-knife conization may be preferred when interpretation of the margins of the histological specimen is imperative.

Chapter 6: Coinfections and comorbidities (continued)

6.10. Noncommunicable diseases

Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for general population *(conditional recommendation, very-low-certainty evidence).*[a]

[a] The WHO Package of Essential Noncommunicable (PEN) disease interventions for primary health care in low-resource settings targets the following populations for cardiovascular disease screening: age older than 40 years, smokers, people with known hypertension or diabetes, waist circumference (>90 cm for women and >110 cm for men) and family history of diabetes or premature cardiovascular disease.

Good practice statement

Strategies for the prevention and risk reduction of cardiovascular diseases by addressing modifiable factors such as blood pressure, smoking, obesity status, unhealthy diet and lack of physical activity should be applied to all people living with HIV.

6.11. Mental health among people living with HIV

Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV *(conditional recommendation, very-low-certainty evidence).*

6.13. Sexually transmitted infections

For men who have sex with men and transgender people

Men who have sex with men and transgender people with symptomatic sexually transmitted infections should seek and be offered syndromic management and treatment.

Offering periodic testing for asymptomatic urethral and rectal *N. gonorrhoeae* and *C. trachomatis* infections using NAAT is suggested over not offering such testing for men who have sex with men and transgender people *(conditional recommendation, low-certainty evidence).*

Not offering periodic testing for asymptomatic urethral and rectal *N. gonorrhoeae* infections using culture is suggested over offering such testing for men who have sex with men and transgender people *(conditional recommendation, low-certainty evidence).*

Offering periodic serological testing for asymptomatic syphilis infection to men who have sex with men and transgender people is strongly recommended over not offering such screening *(strong recommendation, moderate-certainty evidence).*

For sex workers and their clients in low- and middle-income countries

WHO suggests offering periodic screening for asymptomatic sexually transmitted infections to female sex workers *(conditional recommendation, low-certainty evidence).*

WHO suggests offering female sex workers, in settings with high prevalence and limited clinical services, periodic presumptive treatment for asymptomatic sexually transmitted infections *(conditional recommendation, moderate- to high-certainty evidence).*

For sex workers and their clients in low- and middle-income countries

The WHO sexually transmitted infection guideline recommends screening all pregnant women for syphilis during the first antenatal care visit *(strong recommendation, moderate-certainty evidence).*

This recommendation applies to all settings, including settings with high or low prevalence of syphilis.

Management of urethral discharge

For people who present with urethral discharge from the penis, management is recommended to be based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit *(strong recommendation, moderate-certainty evidence).*

Chapter 6: Coinfections and comorbidities (continued)

Management of vaginal discharge

For people who present with vaginal discharge, WHO recommends treatment for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis* on the same visit. WHO suggests treatment based on the results of quality-assured molecular assays for *N. gonorrhoeae* and/or *C. trachomatis* and/or *T. vaginalis*. In settings in which treatment based on the results of molecular assay in the same visit is not feasible or that have limited or no molecular testing, WHO suggests treatment based on testing with quality-assured rapid point-of-care tests or on syndromic treatment *(strong recommendation, moderate-certainty evidence).*

WHO suggests treating for bacterial vaginosis if vaginal discharge is present (for example, tenacious or thin) or based on the results of microscopy, if available *(conditional recommendation low-certainty evidence).*

WHO suggests treating for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available *(conditional recommendation low-certainty evidence).*

For management of women with lower abdominal pain

For sexually active women who present with lower abdominal pain, WHO suggests assessing for pelvic inflammatory disease and treating syndromically.

WHO suggests the following.

- Treat for pelvic inflammatory disease on the same visit.
- Test for infection with *N. gonorrhoeae* and *C. trachomatis* and, if available, *Mycoplasma genitalium*, to support partner management when tests are available *(conditional recommendation, low-certainty evidence).*

Management of genital ulcer disease, including anorectal ulcers

For people who present with genital ulcers (including anorectal ulcers), WHO recommends treatment based on quality-assured molecular assays of the ulcer. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit *(strong recommendation, moderate-certainty evidence).*

Management of anorectal discharge

For people who present with anorectal discharge and report receptive anal sex, WHO recommends management based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit *(strong recommendation, moderate-certainty evidence).*

Good practice for men includes:

- taking a medical and sexual history and assessing risk for sexually transmitted infections;
- performing a physical examination of the genital and anal areas;
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines;
- if symptoms persist at review, good practice includes checking partner notification and treatment history; and
- for people with recurrent or persistent urethral discharge, referring people to a centre with laboratory capacity to diagnose infection with *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium*.

Chapter 6: Coinfections and comorbidities (continued)

Good practice for women includes:

- taking a medical and sexual history and assessing risk for sexually transmitted infections;
- performing a physical examination, including abdominal and pelvic examination to assess for pelvic inflammatory disease, surgical conditions or pregnancy and external vulvo-vaginal examination to visualize any lesions, overt genital discharge or vulval erythema and excoriations;
- bimanual digital examination of the vagina to (1) assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove;
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and
- for people with recurrent or persistent vaginal discharge, referring to a centre with laboratory capacity to diagnose infection with *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, *T. vaginalis* and bacterial vaginosis and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium* (if there is a test) or for a specialist's assessment (sexually transmitted infection expert and physician or a gynaecologist), when no such testing is available in primary health care centres.

6.16.1 Infant feeding in the context of HIV

Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (similar to the general population) while being fully supported for ART adherence (see Chapter 7 for interventions to optimize adherence) *(strong recommendation, low-certainty evidence for 12 months; very-low-certainty evidence for 24 months)*.[a]

[a] WHO-recommended breastfeeding is defined as: (1) initiating breastfeeding within the first hour of life; (2) exclusive breastfeeding for the first six months of life (that is, the infant only receives breast-milk without any additional food or drink, not even water); followed by (3) continued breastfeeding for up to two years of age or beyond (with the introduction of appropriate complementary foods at six months); and (4) breastfeeding on demand – that is, as often as the child wants, day and night.

Remarks

The Guideline Development Group agreed that this recommendation should be framed as follows. In settings in which health services provide and support lifelong ART, including adherence counselling, and promote and support breastfeeding among women living with HIV, the duration of breastfeeding should not be restricted. Further, mothers living with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter and continue breastfeeding. Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided.

This recommendation updates the component of the 2010 recommendation on which breastfeeding practices and for how long related to the duration of breastfeeding. The components of the 2010 recommendation on breastfeeding practices and stopping breastfeeding remain unchanged and valid.

When mothers living with HIV do not exclusively breastfeed

Good practice statement

Mothers living with HIV and health-care workers can be reassured that ART reduces the risk of postnatal HIV transmission in the context of mixed feeding. Although exclusive breastfeeding is recommended, practising mixed feeding is not a reason to stop breastfeeding in the presence of ARV drugs.

When mothers living with HIV do not plan to breastfeed for 12 months

Good practice statement

Mothers living with HIV and health-care workers can be reassured that shorter durations of breastfeeding of less than 12 months are better than never initiating breastfeeding at all.

Chapter 7: Service delivery

7.2 Linkage from HIV testing to enrolment in care

Following an HIV diagnosis, a package of support interventions should be offered to ensure timely linkage to care for all people living with HIV *(strong recommendation, moderate-certainty evidence)*.

The following interventions have demonstrated benefit in improving linkage to care following an HIV diagnosis:

- streamlined interventions to reduce time between diagnoses and engagement in care including (i) enhanced linkage with case-management; (ii) support for HIV disclosure; (iii) tracing; (iv) training staff to provide multiple services, and (v) streamlined services *(moderate-certainty evidence)*;
- peer support[a] & navigation approaches for linkage *(moderate-certainty evidence)*; and
- quality improvement approaches using data to improve linkage *(low-certainty evidence)*.

[a] Includes peer counselling.

Good practice statement

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations. It should promote the engagement and support of people and families to play an active role in their own care through informed decision-making.

Good practice statement

All people newly diagnosed with HIV should be retested to verify their HIV status before starting ART, using the same testing strategy and algorithm as the initial test. To minimize the risk of misdiagnosis, this approach should be maintained in settings in which rapid ART initiation is being implemented.

Good practice statement

The introduction of the "treat all" recommendation (ART for all people living with HIV regardless of CD4 cell count) supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication.

Good practice statement

People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation. Rapid start of ART is especially important for people with very low CD4 cell counts, among whom the risk of death is high. People should not be coerced to start immediately and should be supported in making an informed choice regarding when to start ART.

7.4 People-centred care

Good practice statement

Health systems should invest in people-centred practices and communication, including ongoing training, mentoring, supportive supervision and monitoring health-care workers, to improve the relationships between patients and health-care providers

Good practice statement

HIV programmes should:

- provide people-centred care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and engage and support people and families to play an active role in their own care by informed decision-making;
- offer safe, acceptable and appropriate clinical and non-clinical services in a timely fashion, aiming to reduce morbidity and mortality associated with HIV infection and to improve health outcomes and quality of life in general; and
- promote the efficient and effective use of resources.

Chapter 7: Service delivery (continued)

7.5 Initiating and maintaining treatment

7.5.1 Initiating ART outside the health facility

ART initiation may be offered outside the health facility *(conditional recommendation, low- to moderate-certainty evidence).*

This recommendation is additional to the routine offer of ART initiation at the health facility.

7.5.2 Rapid initiation of ART, including same-day start

Rapid ART initiation[a] should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment *(strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).*

[a] Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start *(strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).*

Good practice statement

The offer of same-day ART initiation should include approaches to improve uptake, treatment adherence and retention such as tailored patient education, counselling and support.

7.5.3 Frequency of clinical visits and ART pick-up

People established on ART should be offered clinical visits every 3–6 months, preferably every six months if feasible[a] (strong recommendation, moderate-certainty evidence).

[a] When routine clinical consultations are due, they should be coordinated with planned medicine pickups to reduce visit frequency.

People established on ART should be offered refills of ART lasting 3–6 months, preferably six months if feasible[b] *(strong recommendation, moderate- to low-certainty evidence).*

[b] ARV supply management should be strengthened to ensure availability of ARV medicine and prevent stock-outs in the context of less frequent medication pickups.

7.5.4 Adherence support

Adherence support interventions should be provided to people on ART *(strong recommendation, moderate-certainty evidence).*

The following interventions have demonstrated effectiveness in improving adherence and virological suppression:

- peer counsellors *(moderate-certainty evidence)*;
- mobile phone text messages *(moderate-certainty evidence)*;
- reminder devices *(moderate-certainty evidence)*;
- cognitive behavioural therapy *(moderate-certainty evidence)*;
- behavioural skills training or medication adherence training *(moderate-certainty evidence)*; and
- fixed-dose combinations and once-daily regimens *(moderate-certainty evidence).*

7.5.5 Monitoring adherence to ART in routine programme and care settings

Good practice statement

Viral load for treatment monitoring should be complemented with non-judgemental, tailored approaches to assessing adherence.

Chapter 7: Service delivery (continued)

7.6 Continuity of care

7.6.1 Retention in care

Programmes should provide community support for people living with HIV to improve retention in HIV care *(strong recommendation, low-certainty evidence).*

The following community-level interventions have demonstrated benefit in improving retention in care:

- package of community-based interventions[a] *(children: low-certainty evidence; adults: very-low-certainty evidence);*
- adherence clubs[b] *(moderate-certainty evidence)*; and
- extra care for high-risk people *(very-low-certainty evidence)*.

[a] Patient advocates, treatment and peer support interventions providing adherence and psychosocial support in the community.

[b] Peer support, distribution of ARV drugs and assessment by non-clinical or lay providers.

7.6.2 Tracing and re-engagement in care

HIV programmes should implement interventions to trace people who have disengaged from care and provide support for re-engagement *(strong recommendation, low-certainty evidence).*

7.7 Task sharing

7.7.1 Task sharing for initiation and maintenance of ART

These recommendations apply to all adults, adolescents and children living with HIV

Trained non-physician clinicians, midwives and nurses can initiate first-line ART *(strong recommendation, moderate-certainty evidence).*

Trained non-physician clinicians, midwives and nurses can maintain ART *(strong recommendation, moderate-certainty evidence).*

Trained and supervised community health workers can dispense ART between regular clinical visits *(strong recommendation, moderate-certainty evidence).*

Trained and supervised lay providers can distribute ART *(strong recommendation, low-certainty evidence).*

7.7.2 Task sharing of specimen collection and point-of-care testing

Task sharing of specimen collection and point-of-care testing with non-laboratory personnel should be implemented when professional staffing capacity is limited *(strong recommendation, moderate-certainty evidence).*

7.8 Decentralization

Decentralization of ART care should be considered as a way to increase access and improve retention in care. The following approaches have demonstrated effectiveness in improving access and retention:

- initiation of ART in hospitals with maintenance of ART in peripheral health facilities *(strong recommendation, low-certainty evidence);*
- initiation and maintenance of ART in peripheral health facilities *(strong recommendation, low-certainty evidence)*; and
- initiation of ART at peripheral health facilities with maintenance at the community level[a] *(strong recommendation, moderate-certainty evidence)*.

[a] Community level includes external outreach sites, health posts, home-based services or community-based organizations. Frequency of clinic visits will depend on health status.

Chapter 7: Service delivery (continued)

7.9 Integrating services

7.9.1 Delivering ART in maternal and child health-care settings

In generalized epidemic settings, ART should be initiated and maintained in pregnant and postpartum women and in infants at maternal and child health care settings, with linkage and referral to ongoing HIV care and ART, where appropriate *(strong recommendation, very-low-certainty evidence).*

7.9.2 Delivering ART in TB treatment settings and TB treatment in HIV care settings

In settings with a high burden of HIV and TB, ART should be initiated in TB treatment settings, with linkage to ongoing HIV care and ART *(strong recommendation, very-low-certainty evidence).*

In settings with a high burden of HIV and TB, TB treatment may be provided for people living with HIV in HIV care settings where a TB diagnosis has also been made *(strong recommendation, very-low-certainty evidence).*

7.9.3 Integrating sexual and reproductive health services, including contraception, within HIV services

Sexually transmitted infection (STI) and family planning services can be integrated within HIV care settings *(conditional recommendation, very-low-certainty evidence).*

Sexual and reproductive health services, including contraception, may be integrated within HIV services *(conditional recommendation, very-low-certainty evidence).* ★

7.9.4 Integrating diabetes and hypertension care with HIV care ★

Diabetes and hypertension care may be integrated with HIV services *(conditional recommendation, very-low-certainty evidence).*

7.9.5 ART in settings providing opioid substitution therapy ★

ART should be initiated and maintained in people living with HIV at care settings where opioid substitution therapy (OST) is provided *(strong recommendation, very-low-certainty evidence).*

7.9.6 Diagnostic integration

Good practice statement

Disease programmes, especially HIV and TB, should actively work towards balanced integration of diagnostic services.

7.11 Service delivery for adolescents

7.11.1 Delivering quality HIV services to adolescents

Adolescent-friendly services should be implemented in HIV services to ensure engagement and improved outcomes *(strong recommendation, low-certainty evidence).*

Community-based approaches can improve treatment adherence and retention in care of adolescents living with HIV *(conditional recommendation, very-low-certainty evidence).*

Chapter 7: Service delivery (continued)

Training of health-care workers can contribute to treatment adherence and improvement in retention in care of adolescents living with HIV *(conditional recommendation, very-low-certainty evidence).*

Adolescents should be counselled about the potential benefits and risks of disclosure of their HIV status to others and empowered and supported to determine if, when, how and to whom to disclose *(conditional recommendation, very-low-certainty evidence).*

7.11.2 Psychosocial interventions for adolescents and young adults living with HIV

Psychosocial interventions should be provided to all adolescents and young adults living with HIV *(strong recommendation, moderate-certainty evidence).*

7.15 Laboratory connectivity

Electronic communication can be considered to transfer test results and reduce delays in acting on the results of infant diagnosis and other essential laboratory tests *(conditional recommendation, low-certainty evidence).*

INTRODUCTION

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1. INTRODUCTION

1.1 Background and rationale

WHO promotes a public health approach to HIV prevention, treatment and care in resource-limited settings *(1)*. These guidelines provide global guidance on the diagnosis of HIV infection, the care of people living with HIV, the use of antiretroviral (ARV) drugs for treating and preventing HIV infection, service delivery and monitoring and evaluation. This edition updates the 2016 WHO consolidated guidelines on HIV *(2)* based on an extensive review of new evidence and consolidates relevant WHO guidance published between 2016 and 2021.

These guidelines promote the importance of promoting a people-centred approach. With the great progress made to improve access to antiretroviral therapy (ART), several populations living with HIV are subject to structural barriers, including stigma, discrimination, criminalization and violence. This is especially important to women, young girls and adolescents and key populations (men who have sex with men, sex workers, people who inject drugs, people in prisons and closed settings and transgender people), who are subject to these barriers across the HIV care cascade *(3)*. These guidelines describe essential strategies for an enabling environment, including developing supportive norms and policies, working towards decriminalizing behaviour, financial commitment and empowering communities. WHO also supports a strong emphasis on workforce training against stigma, discrimination and violence to ensure that all populations benefit from accessing better and safer health-care services. Updated and consolidated guidance for key populations is being developed to further strengthen existing enabling, clinical and service delivery recommendations and is expected to be available in 2022.

These consolidated guidelines on HIV include all currently valid WHO guidelines, guidance and good practice statements across the HIV care cascade. The recommendations include reference to the source guideline.

Implementing the recommendations and approaches in these guidelines will have important implications for programme priority setting, funding and service delivery at the national and global level.

1.2 Objectives

These guidelines contribute to achieving the Triple Billion targets of 1 billion more people benefitting from universal health coverage, 1 billion more people better protected from health emergencies and 1 billion more people enjoying better health and well-being *(4)*. These guidelines are also expected to help meet UNAIDS commitments and the 95–95–95 targets *(5)*.

The objectives of these guidelines are:

- to provide updated, evidence-informed clinical recommendations outlining a public health approach to providing ARV drugs for HIV prevention and treatment for all age groups and populations in the context of the continuum of HIV care, with a focus on settings with limited health system capacity and resources;
- to provide guidance on key operational and service delivery issues that need to be addressed to increase HIV prevention, testing and treatment access, strengthen the continuum of HIV care and further integrate the provision of ARV drugs into health systems; and

- to provide programmatic guidance for decision-makers and planners at the national level on adapting, setting priorities for and implementing the clinical and operational recommendations and monitoring their implementation and impact.

1.3 Target audience

The guidelines are primarily intended for use by national HIV programme managers. They will also be of interest to the following audiences:

- national HIV treatment and prevention advisory boards;
- national TB programme managers;
- national hepatitis programme managers;
- managers of maternal, newborn and child health and sexual and reproductive health and noncommunicable disease programmes (including mental health and substance use);
- clinicians and other health service providers;
- managers of national laboratory services;
- people living with HIV and community-based organizations;
- key population networks; and
- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in resource-limited settings.

1.4 Guiding principles

The following principles have informed the development of these guidelines and should guide the implementation of the recommendations:

- The implementation of the guidelines should contribute to realizing the Sustainable Development Goals and Triple Billion targets.
- The guidelines are based on a public health approach to scaling up the use of ARV drugs along the continuum of HIV prevention, treatment, care and support.
- The recommendations within these guidelines should be implemented with a view to strengthening broader health systems, especially primary and chronic care.
- Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.
- Implementation of the guidelines needs to be accompanied by efforts to promote an enabling environment and protect the human rights of people who need HIV services, including ensuring informed consent, preventing stigma and discrimination in the provision of services, addressing laws and legislation that criminalize the behaviour of people and promoting gender equity.
- The development and implementation of the guidelines should realize the rights and responsibilities of people living with HIV and promote the greater involvement of people living with HIV and meaningful involvement of people living with HIV principles.

1.5 Methods for developing the guidelines

1.5.1 Guideline contributors

These consolidated guidelines are a compilation of recommendations published between 2016 and 2021. All guidelines included have been developed in accordance with procedures established by the WHO Guidelines Review Committee *(6)*. The recommendations in the guidelines are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to reviewing evidence and formulating recommendations *(7)*. Consistent with previous WHO guidelines, these guidelines are based on a public health approach that considers feasibility and effectiveness across a variety of settings. For each recommendation, the systematic reviews and evidence-to-decision-making tables, prepared in accordance with the GRADE process, were shared in advance and presented at the meetings, and the methodologist facilitated discussions. The methods, evidence and supporting information for each recommendation are available in the guideline in which it was originally published and cross-referenced in these consolidated guidelines.

The composition of the guideline development groups was in accordance with WHO procedures for developing guidelines *(6)* and included a range of representation from HIV experts, researchers, programme managers, epidemiologists, human rights experts, representatives of civil society organizations and networks of people living with HIV. The WHO HIV Civil Society Reference Group plays a role in advising on the selection of representatives from civil society. In selecting members, appropriate representation by region and gender is considered. The membership of the external review groups is selected to provide further geographical representation.

1.5.2 Competing interests

All external contributors to the development of guidelines collated here, including members of the guideline development groups and the external review groups, completed a WHO declaration of interests form. In accordance with the WHO declaration of interests policy for experts, a brief biography of all guideline development group members is published on the WHO HIV website for a period of 14 days prior to the guideline meeting.

The responsible technical officers for developing guidelines reviewed all the declaration of interests forms completed by the guideline development group members. A management plan for each declared conflict was agreed and recorded at the time of the meetings. All declared interests and management strategies were discussed with the chairs and methodologist for the respective meetings. Declared conflicts are shared at the start of each guideline development group meetings, and participation in decision-making where a potential conflict was involved is closely monitored by the WHO Guideline Steering Group and GRADE methodologist.

Every effort is made to ensure that any potential influence of conflicts of interest is minimized. The Guideline Steering Group assessed all completed declaration of interests forms for other external contributors to the guidelines. Individual participation was reviewed with regard to the interests declared. All declaration of interests forms are on electronic file at the WHO Department of Global HIV, Hepatitis and Sexually Transmitted Infections Programmes and will be maintained for 10 years.

Funding from the Bill & Melinda Gates Foundation, the United States President's Emergency Plan for AIDS Relief, the United States Agency for International Development, the United States Centers for Disease Control and Prevention and Unitaid supported the development of these guidelines.

1.5.3 Evidence synthesis

This publication summarizes guidelines that have already been published and compiles previously formulated recommendations. Typically, the process of developing recommendations begins with consultative meetings with experts, health ministries and communities, with research questions being developed and priorities set. A WHO steering group develops questions for systematic reviews using a PICO (population, intervention, comparator, outcomes) format. For WHO recommendations included in this publication, a GRADE approach *(7)* was used to appraise relevant evidence and was placed into an evidence-to-decision framework to help inform the discussions at guideline development group meetings.

1.5.4 Peer review

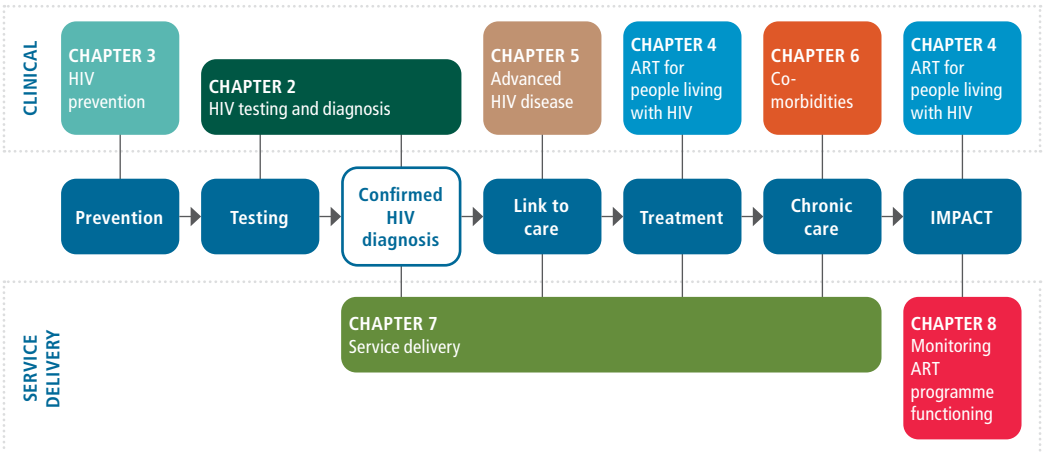
External peer review was conducted in accordance with WHO standards for all the individual guidelines included in this consolidated publication. An invited review group comprising broad expertise in public health, programme management and community representation reviewed a draft and provided comments on the validity, reliability and clarity of the content.

1.6 Organization of the guidelines

1.6.1 Chapter contents

The structure of the guidelines is based on the continuum of HIV testing, prevention, treatment and care (Fig. 1.1).

Fig. 1.1 Continuum of care and relevant sections of the guideline



The chapters of the guidelines include the following information.

Chapter 2 summarizes existing WHO guidance on HIV testing services, including information to be provided during pre- and post-test counselling, approaches to service delivery and considerations for priority populations. New recommendations on the timing of and approaches to virological testing among infants and the use of new testing technologies are also provided.

Chapter 3 addresses the use of ARV drugs for HIV prevention. A new recommendation on the introduction of the dapivirine vaginal ring as an HIV combination prevention option for women with substantial risk of HIV infection is included *(8,9)*. Recommendations on oral pre- and post-exposure prophylaxis, including infant ARV drug prophylaxis, are summarized and the importance of combination HIV prevention approaches is discussed.

Chapter 4 addresses ART for people living with HIV, including when to start treatment (first-line regimens for adults, adolescents and children) and what regimens to switch to (second- and third-line treatment). The chapter contains key recommendations on rapid ART initiation, the introduction of dolutegravir (DTG) as the preferred option in first-line regimens and in second-line regimens (if not previously used in first-line ART). Updated recommendations on the timing of ART for people with TB and infant feeding by women with HIV are summarized. The chapter includes new recommendations on the use of new point-of-care technologies for viral load testing and treatment monitoring as well as a detailed summary of guidance on managing toxicity related to ARV drugs and key ARV drug–drug interactions.

Chapter 5 summarizes the package of care for people with advanced HIV disease and the clinical management of cryptococcal disease and histoplasmosis. This package of advanced HIV care includes screening for TB, providing TB preventative therapy, testing and pre-emptive treatment for cryptococcal disease, providing co-trimoxazole and enhanced adherence counselling. It also links to the new WHO systematic screening guidance for TB and the most recent WHO guidance for TB preventive therapy.

Chapter 6 summarizes existing WHO guidance on the management of common coinfections and comorbidities associated with HIV, including the use of co-trimoxazole preventive therapy, TB case finding and treatment of latent and active TB and managing viral hepatitis. The chapter includes a new section on cervical cancer that introduces new recommendations and good practice statements on screening and treatment of cervical precancerous lesions among women living with HIV. New recommendations are presented for the diagnosis and management of HIV and Buruli ulcer coinfection and treatment of HIV and visceral leishmaniasis coinfection. The importance of assessing and managing the risk of noncommunicable diseases among people living with HIV is highlighted by recommendations on assessing and managing cardiovascular disease and mental health disorders.

Chapter 7 discusses key service delivery issues related to providing ART with a greater focus on person-centred care. Reduced frequency of clinic visits and medication refills for people established on ART and more convenient and accessible ARV drug distribution approaches are recommended to further reduce the burden on clients and health facilities. New recommendations are also provided to help strengthen linkage to care following HIV diagnosis and long-term retention in care, including community-based approaches to support adherence. Integration of sexual and reproductive health and rights services with HIV services has been revalidated, and a new recommendation on integrating noncommunicable disease services with HIV services has been made. Guidance on task sharing, integration and decentralization of services is summarized with new guidance on task sharing and integration of diagnostic services. New guidance in this chapter emphasizes the importance of providing psychosocial support interventions to meet the particular needs of adolescents. The chapter reiterates the importance that the health interventions for key populations, which do not differ from those for other people at risk of or living with HIV, reach these groups, whose access is often compromised, and the approaches for delivering services may therefore need to be adapted.

Chapter 8 summarizes a range of recommended approaches to monitoring and evaluating programmes along the continuum of testing, prevention and care, including using recommended programme indicators and strategies to monitor ARV toxicity and ARV drug resistance.

Chapter 9 outlines the processes for disseminating these new guidelines.

The **annexes** include reference tables to support key recommendations.

Supplementary materials will be forthcoming.

1.6.2 Presentation of the recommendations

Recommendations are typically presented in the following format to reflect the review of the evidence and other considerations by the guideline development groups and have been summarized where appropriate.

- **Recommendation.** The recommendation and the strength and certainty of evidence assessed using the GRADE method are stated.
- **Background.** Previous WHO guidance in this area and developments since the recommendations were last reviewed are described. When the recommendation relates to a specific population, key issues for that population may be briefly summarized.
- **Rationale and supporting evidence.** New evidence on which the recommendation is based and other key operational and programmatic considerations that informed the development of the recommendation is summarized.
- **Implementation considerations.** Key implementation issues specific to the recommendation are discussed.
- **Research gaps.** Issues requiring further research are summarized.

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HIV TESTING AND DIAGNOSIS

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2. HIV TESTING AND DIAGNOSIS

2.1 Introduction

The 2019 consolidated guidelines on HIV testing services bring together the latest evidence-informed guidance and recommendations for delivering high-impact HIV testing services, including linkage to HIV prevention and treatment, in diverse settings and populations *(1)*. A key objective of these guidelines is to encourage greater national and global commitment to implementing effective and efficient HIV testing services as a vital element of the national and global HIV responses. These guidelines also provide operational guidance on demand creation and messaging for HIV testing services; implementation considerations for priority populations; HIV testing strategies for diagnosing HIV; optimizing the use of dual HIV and syphilis rapid diagnostic tests; and considerations for strategic planning and rationalizing resources such as optimal time points for maternal retesting. These 2021 consolidated HIV guidelines also incorporate additional recommendations and considerations for improved infant diagnosis.

2.2 HIV testing for a changing epidemic

People's knowledge of their own HIV status and that of their partners is essential to the success of the HIV response *(1)*. HIV testing services provide a pathway to HIV prevention, treatment, care and other support services. HIV testing services refer to the full range of services that should be provided with HIV testing, including counselling (pre-test information and post-test counselling); linkage to appropriate HIV prevention, treatment, care and other clinical services; and coordination with laboratory services to support quality assurance and the delivery of accurate results *(1)*.

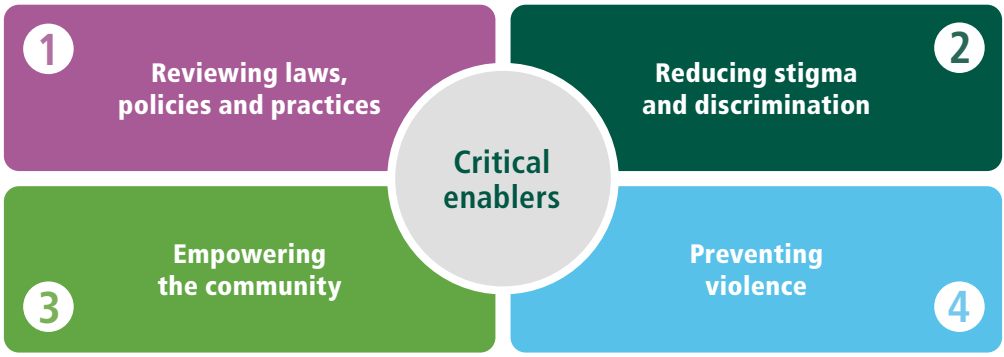
The overarching goals of HIV testing services are to:

- identify people living with HIV by providing high-quality testing services for individuals, couples and families;
- effectively link individuals and their families to HIV treatment, care and support and to HIV prevention services, based on their status; and
- support the scale-up of high-impact interventions to reduce HIV transmission and HIV-related morbidity and mortality.

All HIV testing services should continue to be provided in accordance with WHO's essential five Cs: consent, confidentiality, counselling, correct test results and connection or linkage to prevention, care and treatment.

HIV testing services should always be voluntary. Protecting and maintaining client confidentiality is important, especially when offering testing as part of partner services and when the pre-test information session includes questionnaires screening for risks, symptoms or indicator conditions. An enabling environment that removes barriers such as stigma, discrimination and criminalization and age-of-consent issues is important for increasing access to and uptake of HIV testing services, especially among those at high ongoing risk and key populations (Fig. 2.1).

Fig. 2.1 Addressing critical enablers for HIV testing services programmes



2.3 Mobilizing demand and pre-test services

Demand creation

The 2019 WHO consolidated guidelines on HIV testing services *(1)* include a new best practice statement on demand creation for HIV testing services. Demand creation and mobilization strategies include activities intended to directly improve an individual's knowledge, attitudes, motivations and intentions to test and to inform the decision to obtain HIV testing services.

Good practice statement on demand creation (2019)

Demand creation to increase HIV testing service uptake and engage those in greatest need of services is a valuable tool for mitigating stigma, discrimination and criminalization. Priorities may need to be set among demand creation approaches, depending on the setting, focus population and available resources, as part of a strategy to reach people living with HIV who do not know their status and who have high HIV-related risk. Many demand creation strategies have been assessed for how they affect HIV testing uptake and the proportion of people living with HIV diagnosed, including the following.

Evidence-informed platforms for delivering demand creation include:

- peer-led demand creation interventions, including mobilization; and
- digital platforms, such as short, prerecorded videos encouraging testing.

Approaches that have showed evidence of increasing demand include:

- advertising specific attributes of HIV testing services;
- brief key messages and counselling by providers (less than 15 minutes);
- messages during couples counselling that encourage testing;
- messages related to risk reduction and economic empowerment, especially for people who inject drugs; and
- motivational messages.

Good practice statement on demand creation (2019) (continued)

Evidence suggests that the following approaches may be less effective for demand creation:

- personal invitation letters;
- individualized content messaging;
- counselling focused on building the relationship between the client and counsellor[1]; and
- general text messages, including SMS.

Some studies report increases in HIV testing service uptake when incentives are offered, but when the use of incentives for demand creation is considered, the benefits and costs should be carefully weighed, such as:

- resource sustainability, especially for providing financial incentives, which may undermine the principles of universal health coverage;
- longer-term behavioural changes associating HIV testing services and other services with incentives weighed against short-term increases in uptake;
- negative effects on equity, because some populations and diseases are given priority; and
- potential to give lower priority to systematically implementing strategies that improve service delivery and reduce barriers and disincentives, such as user charges associated with accessing health-care services more broadly.

Source: *Consolidated guidelines on HIV testing services, 2019 (1)*.

2.3.1 Pre-test services

WHO does not recommend pre-test counselling. Instead, programmes should provide concise pre-test information for individuals receiving HIV testing services, their families and their partners in a process that provides relevant information and answers clients' questions. Box 2.1 summarizes the core approaches and strategies of a pre-test service delivery package. With the introduction of additional approaches to HIV testing services, including HIV self-testing and partner services (especially provider-assisted referral and social network–based approaches), tailored, client-centred messaging has become more frequently given priority *(2)*.

See Chapter 3 of the *Consolidated guidelines on HIV testing services, 2019 (1)*, which describes in detail the key considerations for mobilizing demand and implementing effective pre-test services, information and messaging.

[1] Often called "therapeutic alliance counselling", this focuses on the relationship between client and provider and on mutually agreed upon goals, assignment of tasks mutually perceived to be effective and relevant, and developing a bond between client and counsellor based on relationship and trust.

Box 2.1. Pre-test service delivery package: core approaches and strategies

Enabling environment

- Protecting confidentiality
- Preventing social harm, stigma, discrimination and criminalization
- Empowering communities
- Ensuring appropriate age-of-consent policy

Mobilization platforms for creating demand

- Peer-delivered, participatory and community-led approaches, such as using peer educators, community groups and faith-based programmes
- Digital tools based on HIV testing services approach, setting and context, including social media, text messages, mHealth, eHealth mass media and other digital media, including short videos

Mobilization strategies for creating demand

- Targeted promotions, advertisements and messaging related to the attributes of a specific HIV testing service, such as unique setting or option, late-night or weekend hours
- Educational programmes (for example, drama, sport-based and faith-centred)
- Counselling strategies (for example, motivational messages)
- Couples-oriented counselling and partner services (including provider-assisted referral and social network–based approaches).

Pre-test information and messages

- Benefits of testing and of available prevention and treatment services
- Explanation of issues and services for those receiving ART seeking further testing, as relevant
- Opportunity to ask questions.

Screening (as relevant)

- Risk-based screening: for example, providing for self-assessment of risk to prompt testing or, in settings with a low burden of HIV infection, offering HIV testing services to people who, when asked, report risky behaviour or concern about potential exposure
- Symptoms and coinfection screening: for example, for TB, sexually transmitted infections and viral hepatitis
- Screening for indicator conditions

Source: *Consolidated guidelines on HIV testing services, 2019 (1).*

2.4 HIV testing service delivery approaches

WHO recommends differentiated HIV testing service delivery approaches in a people-centred approach to address the needs of a variety of population groups, contexts and epidemic settings (Chapter 7 provides further details on people-centred care and differentiated service for HIV treatment). It is essential for countries to provide a strategic mix of WHO-recommended differentiated HIV testing service delivery approaches (Box 2.1). These include facility-based testing, community-based testing, HIV self-testing, partner services including provider-assisted referral and social network–based approaches. Trained lay providers and peers can now often provide an HIV diagnosis within a single visit in a health facility or community setting using rapid diagnostic tests.

Programmes need to routinely review and use their data to select and optimize the implementation of HIV testing service delivery approaches to reach populations and geographical settings with the largest proportion of people living with HIV who do not know their status.

See Chapter 5 of the *Consolidated guidelines on HIV testing services, 2019 (1)*, which describes in detail the service delivery approaches for HIV testing services.

2.4.1 Facility-based HIV testing services

Recommendations[a]

High-HIV-burden settings

HIV testing should be offered to all populations and in services (for example, services for sexually transmitted infections, hepatitis, TB, children under five, immunization, malnutrition, antenatal care and all services for key populations) as an efficient and effective way to identify people with HIV.

Low-HIV-burden settings

HIV testing should be offered for:

- **adults, adolescents or children who present in clinical settings with signs and symptoms or medical conditions that could indicate HIV infection, including TB, viral hepatitis and sexually transmitted infections;**
- **HIV-exposed children and symptomatic infants and children;**
- **key populations and their partners; and**
- **pregnant women.**

[a] These recommendations were developed in 2007 and revised in 2019.

Source: *Consolidated guidelines on HIV testing services, 2019 (1)*.

Facility-based HIV testing services encompass testing in a health facility or laboratory setting. Facility-based HIV testing services can be provided at stand-alone HIV testing services sites (often referred to as voluntary counselling and testing sites) or routinely offered at clinical sites (often referred to as provider-initiated testing and counselling).

Routine facility-based HIV testing services can be offered at a range of public and private health facilities. This aims to increase the coverage of HIV testing services, provide earlier diagnosis, normalize HIV testing, remove the need for personal motivation to seek HIV testing services and reduce missed opportunities for HIV testing services. HIV testing services have been successfully and effectively integrated in some clinical settings such as antenatal care and TB services. Significant opportunities exist for integrating HIV testing services into many clinical services. The decision where and in which facilities to routinely offer HIV testing services should be guided by the local epidemiology and HIV testing services coverage gaps.

2.4.2 Facility-based HIV testing for infants and children

Recommendations (2016)

- **In settings with a high burden of HIV infection, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV** *(strong recommendation, low-certainty evidence)*.
- **In settings with a high burden of HIV infection, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics** *(conditional recommendation, low-certainty evidence)*.

Good practice statement (2016)

- **In all settings, the biological children of a parent living with HIV (or who may have died from HIV) should be routinely offered HIV testing services and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention and offered a broader package of voluntary provider-assisted referral.**

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3).*

Background

Access to infant diagnosis is mostly limited to infants born to mothers enrolled and retained in programmes to prevent the mother-to-child transmission of HIV. These women generally have very low vertical transmission rates, so most infants diagnosed will test negative. By contrast, mothers who receive inadequate or no interventions to prevent mother-to-child transmission will have much higher transmission rates and yet their infants are unlikely to be tested and identified as HIV-infected. This contributes to the large gap between coverage of and need for ART among children and persistently high HIV-related mortality among children. Previous WHO guidelines have emphasized the importance of case-finding and testing outside programmes to prevent mother-to-child transmission to identify children who did not benefit from such interventions, but for a variety of reasons facility-based[2] testing and counselling for children has not been optimally implemented *(4)*.

[2] Referred to at the time as provider-initiated testing and counselling.

Rationale and supporting evidence

A systematic review was undertaken to compare the standard approach of testing infants and children in programmes to prevent mother-to-child transmission with testing in a range of clinical settings outside such programmes *(5)*. The primary outcomes examined were yield of testing in terms of the HIV seropositivity rate and acceptability by caregivers. The objective was to provide additional evidence to reinforce and contextualize guidance on testing children for HIV.

No studies directly compared the yield of testing within programmes to prevent mother-to-child transmission with testing outside of these programmes. However, 24 studies were identified that reported on the yield of facility-based testing and counselling for children younger than five years in a variety of settings, including inpatient, outpatient, nutritional rehabilitation centres and immunization clinics. Twenty-two of the 24 studies were conducted in sub-Saharan Africa, and 18 of 22 were in settings with high HIV prevalence (>5%). There was one study from Asia and one from Oceania. One study provided data for both outpatient and immunization clinics *(6)*, but the rest assessed yield in only one setting (16 inpatient studies, 2 outpatient studies, 3 nutrition centres and 2 immunization clinics).

One third of the studies were conducted during or after 2013, when WHO issued guidance on using lifelong ART for all pregnant and breastfeeding women. The yield of positive test results was very high in inpatient settings for children (22.5%, 95% confidence interval (CI) 16.0–29.0%) and high in nutrition centres (14.2%, 95% CI 2.3–26.1%). The rates were lower in immunization clinics (3.3%, 95% CI 0–6.9%) and outpatient settings (2.7%, 95% CI 0.3–5.2%). Positivity rates varied significantly by geographical region. Across 18 studies in eastern and southern Africa, the prevalence was 22.6% (95% CI 17.2–28.0%), whereas in four studies conducted in western and central Africa (where the population HIV prevalence is lower), the prevalence was less than half, at 9.7% (95% CI 2.2–17.2%). Asia and Oceania had too few studies to perform subgroup analysis.

Eight studies were identified that used a universal testing approach in inpatient settings for children; these were compared with eight studies that assessed symptoms to determine which children to test. Although symptom-based testing approaches showed a slightly higher yield of positive results (23.1%, 95% CI 14.9–31.3% versus 21.9%, 95% CI 12.4–31.4%) this difference was not statistically significant.

Data from countries with lower prevalence were limited, but one study from western Africa reported a positivity rate of 25% in nutritional centres *(7)*, suggesting that if the coverage of maternal ARV drugs used to prevent mother-to-child transmission is poor, the yield of facility-based testing and counselling of children in selected settings may be high, even when the overall HIV prevalence in the country is low. Unpublished data from Ethiopia suggest that prevalence rates among children – even in inpatient settings – have declined significantly over the past 10 years, but testing of children of index clients has remained consistently high at greater than 5% (T. Tsague, UNICEF, personal communication, June 2015).

There are no reports on the cost–effectiveness of testing children for HIV in specific health-care settings for children. Integrating HIV services (including HIV testing) into other health programmes has been found to be generally cost effective, but the cost–effectiveness of facility-based testing and counselling for children (especially in immunization programmes and outpatient clinics, where the yield of positive results is likely to be lower) depends on factors such as maternal prevalence and the coverage of services to prevent mother-to-child transmission *(8)*. In settings with high maternal HIV prevalence and low coverage of services to prevent mother-to-child transmission, testing infants and children is likely to be highly cost effective as a strategy to prevent HIV-associated mortality. Moreover, facility-based testing and counselling during infancy may identify infants who are exposed to HIV with detectable antibodies but are not yet infected, providing an opportunity to prevent transmission during breastfeeding.

Of the 24 studies assessed in the systematic review, 13 reported on the rates of caregiver acceptance of HIV testing children. Acceptance rates varied by the location of testing and by region, but the overall mean acceptance rate was high, at 92% (range 73–100%). Most caregivers were motivated to accept testing by a desire to know the child's HIV status (78%). A small minority (5%) reported being influenced by other parents whose children had been tested. In a study in South Africa to inform about the acceptability and feasibility of routine HIV testing in immunization clinics, just over half of all eligible children and caregivers accepted HIV testing *(9)*. The Guideline Development Group made a strong recommendation to provide routine HIV testing for infants and children admitted for inpatient care or attending malnutrition clinics, citing existing vast programme experience and testing yield along with high levels of feasibility and acceptability, despite the low-certainty evidence.

Implementation considerations

Although the guidance for active case finding and facility-based testing and counselling among children has been in place since 2007, the uptake of this recommendation has been poor. Issues around the legal age of consent and provider discomfort with disclosure have contributed to this lack of uptake, especially for adolescents and older children. A recent study in six primary clinics in Zimbabwe identified several other factors, including a perceived lack of importance attached to testing older children and a sense that testing was not warranted if children were asymptomatic *(10)*. Lack of time and reagents and discomfort with approaching male caregivers were also noted as reasons for not testing. A WHO survey of health workers, policy-makers and programme managers from 17 countries found that almost half the respondents thought that testing children in immunization clinics would be either easy or very easy to do, suggesting that this policy is highly feasible to implement. Experience from countries that have been trying to roll out facility-based testing and counselling of children highlights the importance of thorough linkage to care and services for children who are exposed or infected. Linkage to care may be easier for children in inpatient settings than for those in busy outpatient clinics. The negative impact of HIV testing on the uptake of other essential childhood interventions, such as immunization, has been cited as an argument against integrating testing in immunization clinics *(11)*. A study in the United Republic of Tanzania showed that, although integration of HIV testing resulted in an increase in immunization rates in urban centres, there was a decrease in rural facilities, possibly reflecting higher levels of stigma in rural communities *(12)*.

2.4.3 Community-based HIV testing services

Recommendations (2019)

High-HIV-burden settings

- **Community-based HIV testing services are recommended, with linkage to prevention, treatment and care services, in addition to routine facility-based testing, for all populations, particularly key populations** *(strong recommendation, low-certainty evidence)*.

Low-HIV-burden settings

- **Community-based HIV testing services are recommended for key populations, with linkage to prevention, treatment and care services, in addition to routine facility-based testing** *(strong recommendation, low-certainty evidence)*.

Source: *Consolidated guidelines on HIV testing services, 2019 (1).*

Community-based testing refers to HIV testing services offered in the community, outside a health facility. WHO recommended community-based HIV testing services in 2013 to expand testing, especially among key populations and their partners, young people, men and others who may be less likely to test in facilities.

Community-based HIV testing services can be delivered in many ways and in different settings and venues. These include HIV testing services at fixed locations in the community, including community-based voluntary counselling and testing sites, mobile outreach in hotspots and community sites such as parks, bars, clubs, cruising sites and saunas and at events, places of worship, workplaces and educational establishments, sometimes with the use of mobile vans. Community-based HIV testing services can also be delivered at peoples' homes, usually referred to as home-based HIV testing services *(1)*. Home-based HIV testing services can either be offered to eligible members in all households in a certain area (that is, door-to-door) or be more focused – for example, in the context of HIV partner services. Community-based HIV testing services can be conducted by trained lay providers and peers using rapid diagnostic tests and the test for triage strategy.

Community-based HIV testing services can be delivered either alone or in combination with testing and screening for other infections such as TB, viral hepatitis and sexually transmitted infections or as part of other community services such as maternal and child health, and contraception. Appropriate training and supervision of providers is needed when combining HIV testing services with other infections and services. Some HIV testing service approaches and models, when carefully designed and focused, can effectively reach priority populations such as men, key populations and the partners of people living with HIV.

2.4.4 HIV self-testing

Recommendations (2019)

HIV self-testing should be offered as an approach to HIV testing services *(strong recommendation, moderate-certainty evidence)*.

Remarks

- Providing HIV self-testing service delivery and support options is desirable.
- Communities need to be engaged in developing and adapting HIV self-testing models.
- HIV self-testing does not provide a definitive HIV-positive diagnosis. Individuals with a reactive test result must receive further testing from a trained tester using the national testing algorithm.

Sources: *WHO recommends HIV self-testing – evidence update and considerations for success (13)* and *Consolidated guidelines on HIV testing services, 2019 (1).*

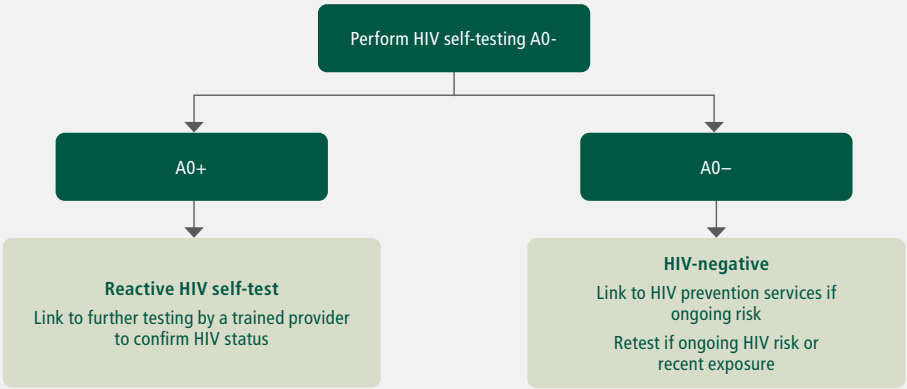
HIV self-testing is a process in which people collect their own specimen (oral fluid or blood) using a simple rapid HIV test and then perform the test and interpret their results when and where they want. Box 2.2 summarizes key messages on HIV self-testing for providers, self-testers and the community.

HIV self-testing has emerged as an effective tool in expanding HIV testing services among people at risk of HIV who may not otherwise test and those at ongoing risk who need to test frequently *(14,15)*. HIV self-testing is a convenient and confidential option for HIV testing. HIV self-testing is safe and accurate, and lay users can perform HIV self-testing and achieve

performance comparable to that of trained health-care workers. Globally, use of HIV self-testing within differentiated national HIV testing services plans has expanded and is helping countries to reach national and global goals.

Box 2.2 Key messages for providers, self-testers and communities

HIV self-testing is a test for triage and does not provide a definitive HIV-positive diagnosis. A reactive (positive) HIV self-testing result is not equivalent to an HIV-positive diagnosis. All reactive HIV self-testing results need to be followed by further testing by a trained provider to confirm HIV status, starting with the first test in the national testing algorithm.



Nonreactive HIV self-testing results should be considered HIV-negative, with no need for immediate further testing except for those starting PrEP. For people starting or already taking PrEP, HIV self-testing will not usually replace initial or subsequent quarterly facility visits and testing.

Those with invalid HIV self-testing results need to repeat the test using another HIV self-testing kit or to seek testing from a trained provider. Any person uncertain about their HIV self-testing result should be encouraged to seek testing from a trained provider.

HIV self-testing is not recommended for people living with HIV who are receiving ART, since false-negative HIV self-testing results can occur. Those who are HIV-positive but not receiving ART should be encouraged and supported to initiate ART.

Retesting following a negative self-test result is necessary only for those at ongoing risk, such as people from key populations and those reporting potential HIV exposure in the preceding 12 weeks.

HIV self-testing means testing yourself. HIV self-testing is for individuals who want to test and learn their HIV status on their own. Offering a HIV self-testing kit to a sexual partner, friend or adult family member and encouraging them to use the self-test can often be a good way to help them learn their HIV status. However, a person should never be coerced or forced to self-test. Coercive or mandatory use of an HIV self-testing kit should never be supported or encouraged and is not considered self-testing.

WHO does not recommend that parents or guardians use HIV self-testing kits to test their babies or children. HIV self-testing will not provide a correct result for children younger than 18 months old because the mother's antibodies may still be present in the infant.

HIV self-testing service delivery models and support tools

HIV self-testing kits can be distributed through various channels, including those supported by public or donor funding or in the private sector as well as through public–private partnerships (Fig. 2.2). If possible, offering choice in HIV self-testing service delivery options and type of test kits (such as between kits using oral fluid or blood) can help to reach more people.

Fig. 2.2 HIV self-testing service delivery models

Community-based

Distribution during campaigns, at events, mobile outreach or home-based (door-to-door) distribution. Integration with existing community-based testing programmes can improve efficiency and optimize resources. Community-led models are likely to be successful.

Facility-based

Distribution from facilities or other fixed sites for use later or within the facilities. Kits can be given to HIV-positive or HIV-negative clients for secondary distribution.

Order online and receive via mail

A range or online platforms such as websites, social media, dating apps, and other digital media can be used. HIV self-testing kits can be provided for free, at a cost or with coupons/vouchers for reduced cost.

Secondary distribution

Includes secondary distribution to partners or peers including distribution by HIV-negative and HIV-positive clients. Index clients can be given HIV self-testing kits by providers of facilities.

Models assessed in RCTs and found effective

Retail outlets, pharmacies and vending machines

Kits are typically provided at a cost to users but price can be reduced through public-private partnerships and distribution of coupons or vouchers.

Faith-best settings

Distribution from faith-based settings such as churches and mosques.

Workplace

Distribution to workers for testing themselves and/or for their partners. Consider sustainable models such as through public-private partnership and/or insurance packages to cover the cost.

Models not assessed in RCTs but can be considered

Many people can perform HIV self-testing correctly with minimal or no support; however, some may need and want support, and it should be made available. This can include video instructions, virtual support or in-person demonstration or training. Providing a range of support options is important, if feasible. Support tools and packages should be adapted to address the local context, population needs and community preferences as well as considering available resources. Programmes are encouraged to define a minimum support package to accompany HIV self-testing implementation. This package can be regularly reviewed and adjusted as programmes expand and scale up. Available resources and community preferences need to be considered.

2.4.5 HIV partner services

Recommendations (2019)

Provider-assisted referral should be offered to people with HIV as part of a comprehensive package of testing and care *(strong recommendation, moderate-certainty evidence)*.

Social network–based approaches can be offered as an HIV testing approach for key populations as part of a comprehensive package of care and prevention *(conditional recommendation, very-low-certainty evidence)*.

Good practice statement (2019)

- **In all settings, biological children with a parent living with HIV (or who may have died from HIV) should be routinely offered HIV testing services and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention and offered a broader package of voluntary provider-assisted referral.**

Note: Partner services include partner notification, contact tracing, index testing and family-based index case testing for reaching the partners of people living with HIV. These guidelines define partner services as encompassing a range of partner services packages and approaches, including social network–based approaches.

Source: *Consolidated guidelines on HIV testing services, 2019 (1).*

Partner services offer voluntary HIV testing services to the sexual and/or drug-injecting partners of people living with HIV. This is an effective way of identifying additional people living with HIV. Partners who are diagnosed with HIV can be linked to treatment services, and those who are HIV-negative and at ongoing risk of acquiring HIV can be linked to effective HIV prevention. When partner services are offered, HIV testing services should also be offered to the biological children of the person living with HIV if the children's HIV status is unknown.

HIV partner services can be delivered in many ways, including patient referral and provider-assisted referral *(16)*. If feasible and acceptable to the client, voluntary provider-assisted referral (see Box 2.3) should be given priority, since it is more effective and provides the opportunity to offer comprehensive prevention interventions to partners who are HIV-negative but remain vulnerable to acquiring HIV.

Box 2.3 Definition of provider-assisted referral

In provider-assisted referral (also called assisted partner notification or index testing), a trained provider asks people living with HIV about their sexual and/or drug-injecting partners and then, with the consent of the HIV-positive client, informs the partners of their potential exposure to HIV. The provider then offers voluntary HIV testing services to these partners. The provider can contact partner(s) by telephone or email or in person and offer them home-based HIV testing services or invite them to visit a facility to receive HIV testing services.

Globally, the adoption of HIV partner services policies and implementation is increasing. Despite progress, members of key populations and their partners do not often fully benefit from HIV partner services and provider-assisted referral *(14,17)*. Although partner services are safe, feasible and effective among members of key populations and their partners *(14,17)*, implementation remains limited. This is often attributed to policy and structural barriers, confidentiality concerns and the reluctance of members of key populations to identify their partners to providers because they fear stigma and discrimination *(17,18)*.

To address some of the challenges in scaling up HIV partner services among key populations, especially the challenges of confidentiality, in 2019 WHO recommended social network–based HIV testing approaches as an approach for reaching the sexual or drug-injecting partners and social contacts of the members of key populations. These approaches also can expand the scope of testing to the HIV-negative partners and social contacts of members of key populations, thus making testing services more acceptable and normalizing their use *(16)*. Social network-based approaches are safe, acceptable and feasible and may identify additional people living with HIV.

All partner services should be voluntary. Whenever partner services and social network–based approaches are offered, the client should be informed of their benefits and cautions and assured that their decisions about contacting partners and other people from their social networks are voluntary and not pressured. Although provider-assisted referral should be encouraged, clients should have the opportunity to choose from all available options for partner services, including social network–based approaches, or to decline it altogether. They can choose different methods for different partners. For example, they may prefer to inform their primary partners themselves (patient referral), but they may not be comfortable informing other partners and instead choose provider-assisted referral.

2.4.6 Strategic planning for HIV testing services

Despite increases in the number of HIV tests conducted every year, 19% of the people living with HIV are unaware of their status and, in many settings, HIV testing services are not sufficiently focused *(19)*. In many settings with high treatment and coverage rates, poorly targeted HIV testing services continue to miss people living with HIV who are at greatest risk and do not know their status. These include key populations globally and, in settings with a high burden of HIV infection in southern Africa, men, adolescents and young people (15–24 years old). These realities require new focus and new approaches to reach people with undiagnosed HIV early in their infection. WHO's 2019 HIV testing services guidelines responds to this changing face of the HIV epidemic *(1)*. They support the development and scale-up of evidence-informed HIV testing services approaches in facilities and in community settings for those who need HIV testing, prevention and treatment services.

Countries need to adopt a strategic mix of service delivery approaches to achieve equitable access to HIV testing services, based on the local context, the nature of the epidemic, priority populations and gaps and available resources. The national HIV testing services plan should facilitate diagnosing as many people living with HIV as early as possible and give priority to reaching the population groups with higher HIV risk in which the gap in knowledge of HIV status is greatest. Once diagnosed, HIV testing services should support effective linkage to appropriate post-test services. People living with HIV who learn their status without adequate support may not link to care or may be lost to follow-up.

Focused HIV testing services approaches are needed, especially in resource-limited settings *(1)*. HIV testing services can be optimized by giving priority to new innovative approaches such as HIV self-testing and partner services, including provider-assisted referral (index testing) and social network–based HIV testing services approaches and focusing them on specific health services, priority populations and geographical settings. Optimized facility-based HIV testing services remain an important approach, especially in settings with a high burden of HIV infection. In addition, community-based testing can effectively reach key populations and other priority groups with a range of delivery models such as through community-based fixed sites or mobile outreach in hotspots and community sites such as parks, bars, clubs, cruising sites and saunas and at events, places of worship, workplaces and educational establishments or through home-based HIV testing services. Test for triage can be used in community-based HIV testing services using trained lay providers or peers and a single rapid diagnostic test and then referring and linking all people with a reactive test result to appropriate HIV prevention, care and treatment services (see also Chapter 7 on linkage from HIV testing to enrolment in care).

For certain population groups, retesting is recommended (see Box 2.4). The primary goal of retesting should be to enable those who have previously tested HIV-negative to stay HIV-negative and to identify those who have become HIV-positive as early as possible so that they can start treatment. Retesting among people who are HIV-negative or of unknown status has two key purposes: (1) monitoring the effectiveness of HIV prevention interventions and (2) identifying and treating new HIV infections as early as possible when prevention efforts fail. Globally, most people who have an HIV-negative test will not need retesting *(1)*.

In low-HIV-burden settings, retesting all pregnant and postpartum women during pregnancy is not advised. In high-HIV-burden settings, retesting is advised for all pregnant women with an unknown or HIV-negative status during late pregnancy (third trimester). Catch-up testing is needed if the first test or retest is missed or delayed. High-HIV-burden countries could consider an additional retest in the postpartum period for specific districts or regions with high HIV burden or incidence, women from key populations or who have a partner with HIV who does not have suppressed viral loads.

See Chapter 7 of the *Consolidated guidelines on HIV testing services, 2019 (1)*, which describes in detail the strategic planning considerations for effective and efficient HIV testing services.

Box 2.4 Suggested optimal retesting frequency for various population groups

All settings

Only specific groups of people in high-HIV-burden settings or individuals with HIV-related risks need post-test counselling messages encouraging retesting at the appropriate intervals. WHO guidance recommends annual retesting for:

- all sexually active individuals in high-HIV-burden settings; and
- people who have ongoing HIV-related risks in all settings, including:
  - key populations, defined as men who have sex with men, people in prison or closed settings, people who inject drugs, sex workers and transgender people;
  - country- or epidemic-specific risk groups such as men and adolescent girls and young women in east and southern Africa; and
  - people with a known HIV-positive partner.

Retesting in special groups: in certain situations, individuals who have been tested for HIV in the past can be retested. These include:

- individuals presenting with a diagnosis or receiving treatment for sexually transmitted infections or viral hepatitis;
- individuals with a confirmed or presumptive TB diagnosis;
- outpatients presenting with clinical conditions or symptoms indicative of HIV; and
- individuals with recent HIV risk exposure.

More frequent retesting, that is, every 3–6 months, may be warranted based on individual risk factors and as part of broader HIV prevention interventions, such as individuals taking PrEP who require quarterly HIV testing or key populations who present to services with a sexually transmitted infection.

Retesting for pregnant and postpartum women

High-HIV-burden settings

Retest all pregnant women with unknown or HIV-negative status in late pregnancy, at the third-trimester visit. If either the first test or retest is missed or delayed, catch-up testing is needed.

An additional retest for women of unknown or HIV-negative status in the postpartum period can be considered. Countries could consider an additional postpartum test in specific districts or provinces with high HIV burden or incidence and among women from a key population or who have partners with HIV who do not have suppressed viral loads.

Box 2.4 Suggested optimal retesting frequency for various population groups (continued)

Low-HIV-burden settings

Retest pregnant women with unknown or HIV-negative status who are in serodiscordant relationships, whose partner does not have suppressed viral loads on ART or have other known ongoing HIV risk in late pregnancy – at a third-trimester visit. If either the first test or retest is missed or delayed, catch-up testing is needed.

An additional retest for women of unknown or HIV-negative status in the postpartum period can be considered among women from key populations or who have partners with HIV who do not have suppressed viral loads. Countries could also consider an additional postpartum test in specific districts or provinces.

Source: *Consolidated guidelines on HIV testing services, 2019 (1).*

2.4.7 Implementation considerations for priority populations

Because of shifts in HIV epidemiology *(20,21)*, all settings must focus efforts increasingly on priority populations that remain underserved by existing approaches (Box 2.5). Priority populations are those that: (1) are most affected by HIV and have high ongoing HIV risk; (2) are critical to achieving and sustaining low HIV incidence; and/or (3) have specific individual or structural HIV-related vulnerabilities *(16)*. Although key populations and their partners are a priority in all settings, other populations may be a priority based on country context, setting or local epidemiology. This often includes men, adolescents and young people, pregnant women, infants and children, serodiscordant couples, sexual and drug-injecting partners of people living with HIV as well as migrants, refugees, displaced populations and other vulnerable groups. See Chapter 6 of the *Consolidated guidelines on HIV testing services, 2019 (1)*, which describes in detail the key considerations for implementing HIV testing services for priority populations.

Box 2.5 Recommendations and implementation considerations for priority populations

Infants and children *(3,22–25)*

Recommendations

The addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis testing approaches can be considered to identify HIV infection among HIV-exposed infants *(conditional recommendation, low-certainty evidence)*.

In settings with a high burden of HIV infection, infants and children with unknown HIV status who are admitted for inpatient care or attending malnutrition clinics should be routinely tested for HIV *(strong recommendation, low-certainty evidence)*.

In settings with a high burden of HIV infection, infants and children with unknown HIV status should be offered HIV testing in outpatient or immunization clinics *(conditional recommendation, low-certainty evidence)*.

Point-of-care nucleic acid testing should be used to diagnose HIV among infants and children younger than 18 months of age *(strong recommendation, high-certainty evidence)*.

Rapid diagnostic tests for HIV serology can be used to assess HIV exposure among infants younger than four months of age. HIV-exposure status among infants and children 4–18 months of age should therefore be ascertained by HIV serological testing the mother *(conditional recommendation, low-certainty evidence)*.

Rapid diagnostic tests for HIV serology can be used to diagnose HIV infection among children older than 18 months following the national testing strategy *(strong recommendation, moderate-certainty evidence)*.

An indeterminate range of viral copy equivalents should be used to improve the accuracy of all nucleic acid–based early infant diagnosis assays *(strong recommendation, moderate-certainty evidence)*.

Good practice statements

National regulatory agencies are encouraged not to delay the adoption of point-of-care early infant diagnosis by conducting further evaluations but instead to adopt a rapid and streamlined registration and national approval process for immediate implementation.

In all settings, biological children with a parent living with HIV (or who may have died of HIV) should be routinely offered HIV testing services and, if found to be either infected or at high risk of infection through breastfeeding, should be linked to services for treatment or prevention and offered a broader package of voluntary provider-assisted referral.

Key populations *(1,26)*

Recommendations

HIV testing services should be routinely offered to all key populations both in the community and in facility-based settings.

Community-based HIV testing, with linkage to prevention, treatment and care, should be offered, in addition to routinely offering testing in facilities, for key populations in all settings *(strong recommendation, low-certainty evidence)*.

Social network–based approaches can be offered as an HIV testing approach for key populations as part of a comprehensive package of care and prevention *(conditional recommendation, very-low-certainty evidence)*.

Adolescents *(26)*

Recommendations

HIV testing services, with linkages to prevention, treatment and care, are recommended for adolescents from key populations *(strong recommendation, very-low-certainty evidence)*.

Adolescents should be counselled about the potential benefits and risks of disclosing their HIV-positive status and empowered and supported to determine whether, when, how and to whom to disclose *(conditional recommendation, very-low-certainty evidence)*.

Settings with a high burden of HIV infection

In settings with a high burden of HIV infection, HIV testing services, with linkage to prevention, treatment and care, are recommended for all adolescents *(strong recommendation, very-low-certainty evidence)*.

Settings with a low burden of HIV infection

HIV testing services, with linkage to prevention, treatment and care, should be accessible to adolescents in low and concentrated epidemics[a] *(conditional recommendation, very-low-certainty evidence)*.

[a] Now referred to as settings with a low burden of HIV infection.

Good practice statement

Governments should revisit age-of-consent policies, considering the need to uphold adolescents' rights to make choices about their own health and well-being *(with consideration for different levels of maturity and understanding)*.

Pregnant women, couples and partners *(1,26,27)*

Recommendations

All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)[a] **at least once and as early as possible** *(syphilis: strong recommendation, moderate-certainty evidence; HBsAg*[a]*: strong recommendation, low-certainty evidence)*.

[a] Particularly in settings with a ≥2% HBsAg seroprevalence in the general population.

Dual HIV and syphilis rapid diagnostic tests can be the first test in HIV testing strategies and algorithms in antenatal care.

Provider-assisted referral should be offered to all people with HIV as part of a voluntary comprehensive package of testing and care *(strong recommendation, moderate-certainty evidence)*.

Couples and partners should be offered voluntary HIV testing services with support for mutual disclosure *(strong recommendation, low-certainty evidence)*.

Women who disclose any form of violence by an intimate partner (or other family member) or sexual assault by any perpetrator should be offered immediate support. Health-care providers should, as a minimum, offer first-line support when women disclose violence. If health-care providers are unable to provide first-line support, they should ensure that someone else (within their health-care setting or another that is easily accessible) is immediately available to do so *(strong recommendation, indirect evidence)*.

Health-care providers should ask about exposure to intimate partner violence when assessing conditions that may be caused or complicated by intimate partner violence, to improve diagnosis and identification and subsequent care *(strong recommendation, indirect evidence)*.

Good practice statements

Mandatory or coercive testing is never warranted. In consultation with the client, the provider should assess the risk of harm, the most appropriate approach for couple and partner testing, including more supportive options such as provider assistance, and situations that make couple or partner testing inadvisable.

2.5 Post-test services and linkage to prevention, treatment and other services

Linkage to appropriate services following HIV diagnosis is a key component of effective and comprehensive HIV testing services. Post-test counselling and other services that lead people to appropriate care should be implemented as part of an explicit linkage strategy. The core package of post-test services includes:

- clear and concise counselling messages;
- referral and offer of rapid ART initiation; and
- additional links to HIV prevention, care, support and other relevant services.

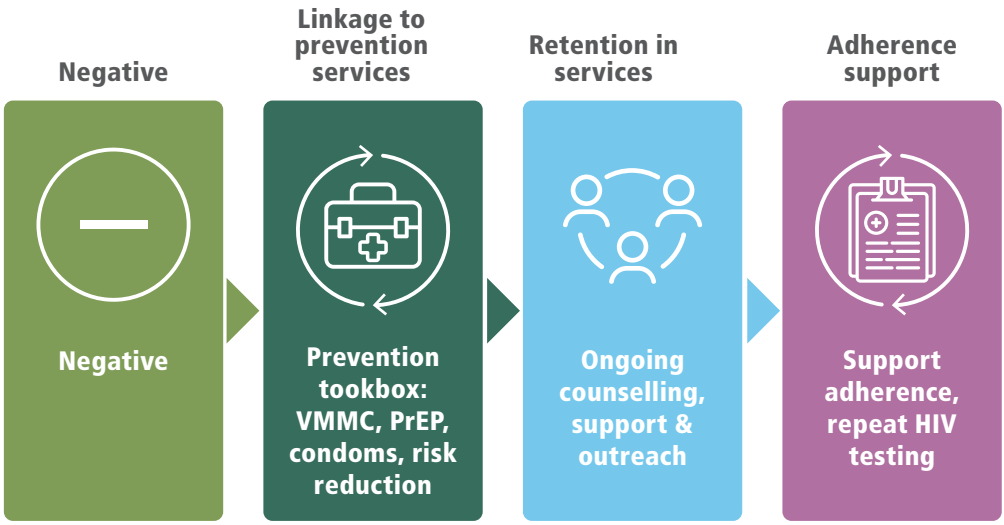
Chapter 7 on service delivery provides further detail on linkage from HIV testing to enrolment in care (see subsection 7.4). Also see Chapter 4 of the *Consolidated guidelines on HIV testing services, 2019 (1)*, which describes in detail the essential post-test service package.

Special considerations for linkage to HIV prevention and other services

Because the number of people living with HIV who do not know their status is declining in many countries, most people testing for HIV are likely to be HIV negative *(5)*. Maximizing programme impact and improving cost–effectiveness requires optimizing service delivery to reach people who are HIV negative but have ongoing risk and to link and retain them in effective prevention services (Fig. 2.3). Once a person is engaged in prevention interventions, HIV testing services will continue to serve as part of prevention monitoring – such as quarterly testing among people taking PrEP – to identify people who are newly infected so they can start ART as soon as possible *(16)*.

See Chapter 3 for recommended HIV prevention approaches.

Fig. 2.3 The HIV prevention continuum



Source: McNairy M and El Sadr W, 2014 *(70)*.

2.6 Strategies to make HIV testing services accessible

Several WHO-recommended health programming practices can improve the accessibility and efficiency of HIV testing services in clinical and community settings, such as integrating HIV testing services with other testing and health services, decentralizing HIV testing services to primary health care facilities and outside the health facilities in the community and task sharing of HIV testing service responsibilities to increase the role of trained lay providers.

Integration

Integration is the co-location and sharing of services and resources across different health areas and includes offering HIV testing, prevention, treatment and care services alongside other relevant health services. WHO recommends integrating HIV services, including HIV testing services, with a range of other relevant clinical services, such as those for TB, viral hepatitis, sexually transmitted infections, maternal and child health, sexual and reproductive health, primary health care, key population programmes such as harm-reduction programmes for people who inject drugs and, in priority countries, voluntary medical male circumcision programmes. The primary purpose of such integration is to make HIV testing services more convenient for people attending health facilities for other reasons and to increase the uptake of HIV testing. Integration is appropriate in all epidemic settings and is especially important where the HIV prevalence is high and should be designed according to the focus populations and context.

Decentralization

Decentralization of HIV testing services refers to providing HIV testing services at peripheral health facilities such as primary health care facilities and outside health facilities in the community. Decentralization of HIV testing services may be appropriate in both high-prevalence and low-prevalence settings. Providing HIV testing in places closer to people's homes may reduce transport costs and the waiting times experienced in central hospitals and thereby increase uptake. For example, community-based HIV testing services may be more attractive for men, young people and key populations, who are otherwise less likely to test in facilities *(3)*. Close collaboration between community programmes conducting HIV testing and nearby health facilities and health-care providers is likely to improve rates of early enrolment in care. Linkage for ART and care services should be provided as quickly as possible, ideally in all decentralized sites and programmes.

Decentralization of HIV testing services may not always be appropriate or acceptable to potential users. In some settings, centralized HIV services may provide greater anonymity than neighbourhood services for key populations or others who fear stigma and discrimination. In some low-prevalence settings, decentralizing HIV testing services may be inefficient and costly. Context, needs, service gaps and overall costs and benefits should be weighed to determine the extent and manner of decentralizing HIV testing services.

Task sharing

Recommendation (2015)

Lay providers who are trained and supervised to use rapid diagnostic tests can independently conduct safe and effective HIV testing services *(strong recommendation, moderate-certainty evidence)*.

Source: *Consolidated guidelines on HIV testing services, 2015 (26).*

Many countries continue to face shortages of trained health workers. Task sharing – the rational redistribution of tasks from types of health-care providers with longer training to types with shorter training – is a pragmatic response to health workforce shortages. Task sharing seeks to increase the effectiveness and efficiency of the available personnel and thus enable the existing workforce to provide HIV testing services to more people.

Trained lay providers and peer workers can support task sharing. A lay provider is defined as any person who performs functions related to health-care delivery and has been trained to deliver specific services but has received no formal professional or paraprofessional certificate or tertiary education degree. Lay providers can be trained to deliver all testing services, including pre-test information, performing HIV rapid diagnostic tests, interpreting test results and reporting HIV status, offering post-test counselling and supporting linkage to prevention, treatment and care services. Peers can be trained to function as lay providers.

WHO recommends that trained and supervised lay providers be able to provide HIV testing services, both in the community and in health facilities. A test-for-triage approach using single rapid diagnostic tests in the community or HIV self-testing with linkage to further testing at facilities can support the role of trained lay providers and community-based HIV testing services.

For further details, see Chapter 7, which includes a strong recommendation on task sharing of specimen collection and point-of-care testing with non-laboratory personnel when professional staffing capacity is limited.

2.7 Maintaining the accuracy and reliability of HIV diagnosis

WHO guidance on HIV diagnosis and testing strategies

Western blotting

Western blotting and line immunoassays should not be used in national HIV testing strategies and algorithms *(strong recommendation, low-certainty evidence).*

HIV testing strategy and algorithm

WHO recommends that all HIV testing algorithms achieve at least 99% positive predictive value and use a combination of tests with ≥99% sensitivity and ≥98% specificity.

The first test in an HIV testing strategy and algorithm should have the highest sensitivity, followed by a second and third test of the highest specificity.

Countries should consider moving to a three-test strategy as HIV positivity within national HIV testing service programmes falls below 5% – meaning all people presenting for HIV testing services should have three consecutive reactive test results in order to receive an HIV-positive diagnosis.

Dual HIV/syphilis rapid diagnostic tests can be the first test in HIV testing strategies and algorithms in antenatal care.

WHO suggests using a testing strategy for HIV diagnosis that is suitable for HIV diagnosis during surveillance and routinely returning HIV test results to participants.

Retesting prior to ART initiation

All people newly diagnosed with HIV should be retested to verify their HIV status prior to starting ART, using the same testing strategy and algorithm as the original diagnosis.

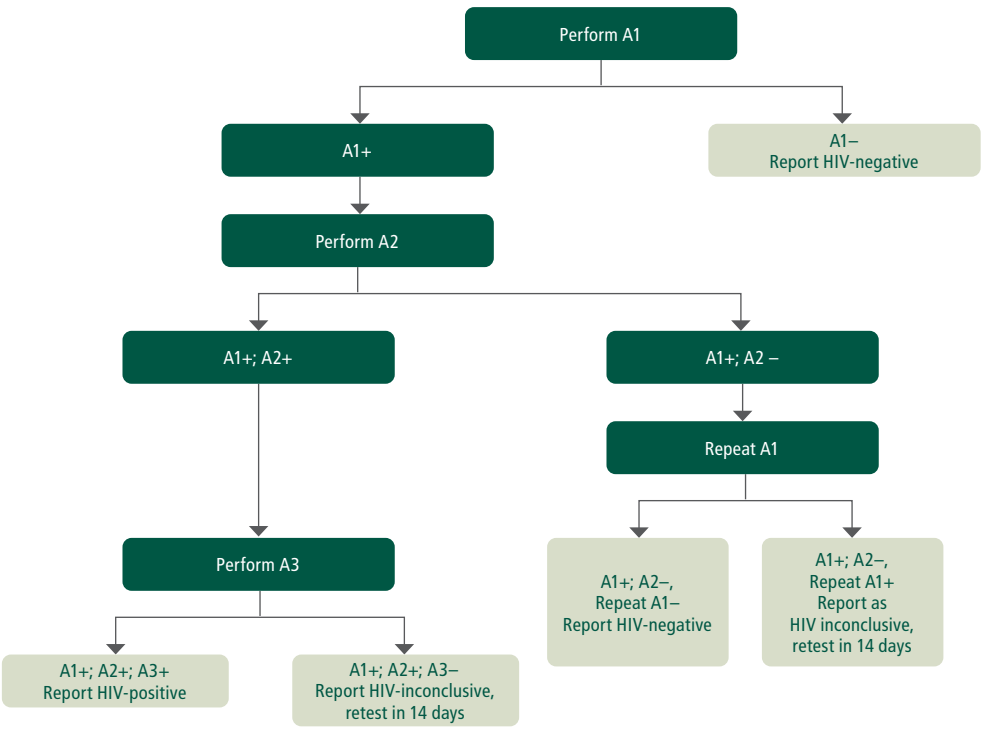
Retesting among people living with HIV who already know their status, who are on treatment, is not recommended as it can provide incorrect results if the person with HIV is on ART.

Source: *Consolidated guidelines on HIV testing services, 2019 (1)*

Providing a correct HIV diagnosis, as quickly as possible, is critical to all HIV testing services and national programmes. Accurate diagnosis enables newly identified people living with HIV to start ART sooner, which has immediate benefits for their health and, through provider-assisted referral (index testing), for the health of their partners and the community *(1)*. To achieve accurate results for children older than 18 months, adolescents and adults, WHO recommends that countries use an HIV testing strategy or algorithm that combines rapid diagnostic tests and enzyme immunoassays that, when used together, achieve a positive predictive value of at least 99% (Fig. 2.4). The positive predictive value indicates the probability that an HIV-positive diagnosis is correct.

WHO encourages all countries to use three consecutive reactive tests to provide an HIV-positive diagnosis. Because of declines in HIV prevalence among those untreated (treatment-adjusted prevalence) and decreasing HIV positivity in HIV testing services programmes, countries currently using two consecutive reactive tests to provide an HIV-positive diagnosis are advised to move toward using three reactive tests as their treatment-adjusted prevalence and national HIV positivity in HIV testing services programmes fall below 5%. Countries with a low burden of HIV infection, with national HIV prevalence below 5%, are reminded to continue to use three consecutive reactive tests to provide an HIV-positive diagnosis.

Fig. 2.4 WHO standard testing strategy for HIV-1 diagnosis (among people ≥18 months of age)



A1:Assay 1 (first test); A2: Assay 2 (second test); A3: Assay 3 (third test). Assay (test) are HIV rapid diagnostic tests (RDTs) or enzyme immunoassays (EIAs).

WHO also recommends that countries move away from using western blotting and line immunoassays in their national testing strategies or algorithms in favour of simpler and less costly rapid diagnostic tests and/or enzyme immunoassays to support the scale-up of HIV testing, prevention and treatment. Using a rapid diagnostic test, a trained lay provider can establish a HIV diagnosis within a single visit in a health facility or community setting *(1)*.

WHO continues to recommend that all programmes retest people diagnosed with HIV prior to initiating lifelong treatment. This retesting to verify an HIV-positive diagnosis is intended to catch human errors such as mislabelling of test results or other random errors related to the test device, lot or testing site *(1)*. Retesting is common among people living with HIV who already know their status, including those receiving treatment. Motivations for retesting vary including doubts about the accuracy of a previous test, feeling sick or healthy or wanting to check on or come to terms with an HIV-positive diagnosis. Such retesting is not recommended and can provide incorrect results if the person living with HIV is receiving ART. For some people who know their HIV status but have not initiated or discontinued treatment, retesting is an important opportunity to initiate or re-engage in care and build trust and gain familiarity with health-care workers and the process of linking to care.

In all settings, dual HIV and syphilis rapid diagnostic tests can be offered as the first test in antenatal care to increase testing and treatment coverage. See Fig 2.5 for WHO-recommended testing strategy for dual detection of HIV and syphilis infection in antenatal care settings.

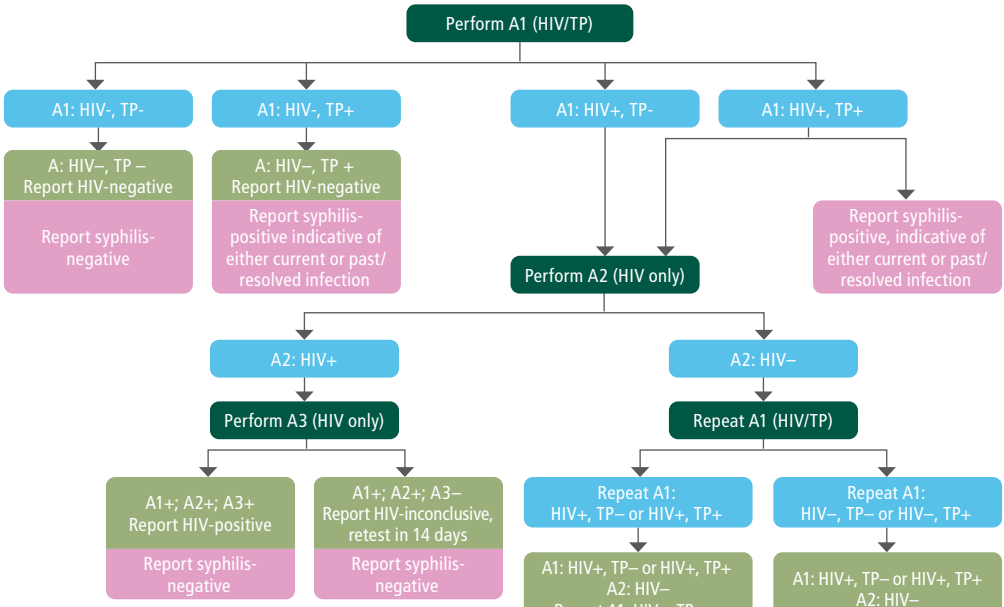
It is important not to use the rapid dual HIV and syphilis test for:

- women with HIV taking ART;
- women already diagnosed with and treated for syphilis during their current pregnancy; and
- retesting for HIV.

See Chapter 8 of the *Consolidated guidelines on HIV testing services, 2019 (1)* for further considerations for selecting diagnostics for HIV diagnosis and use of dual HIV and syphilis rapid diagnostic tests in antenatal care.

In addition, quality assurance implemented through quality management systems is essential for any testing service, ranging from HIV testing conducted in laboratories and health facilities to community-based settings, including rapid diagnostic tests performed by lay providers. Detailed guidance on quality systems is provided in Chapter 9 of the *WHO consolidated guidelines on HIV testing services, 2019 (1)* and other relevant publications *(28,29)*.

Fig. 2.5 WHO-recommended testing strategy for dual detection of HIV and syphilis infection in antenatal care settings



A1:Assay 1, A2: Assay 2, A3: Assay 3, TP: *Treponema pallidum* (syphilis).

A1 (Assay 1) is a dual HIV/syphilis rapid diagnostic test (RDT).

A2 and A3 (Assay 2 and Assay 3) are HIV RDTs or enzyme immunoassay (EIAs).

When resolving discrepant results, all reactive TP (syphilis) results, including A1:TP+ or Repeat A1: TP+, should be referred for treatment and further testing according to national guidelines.

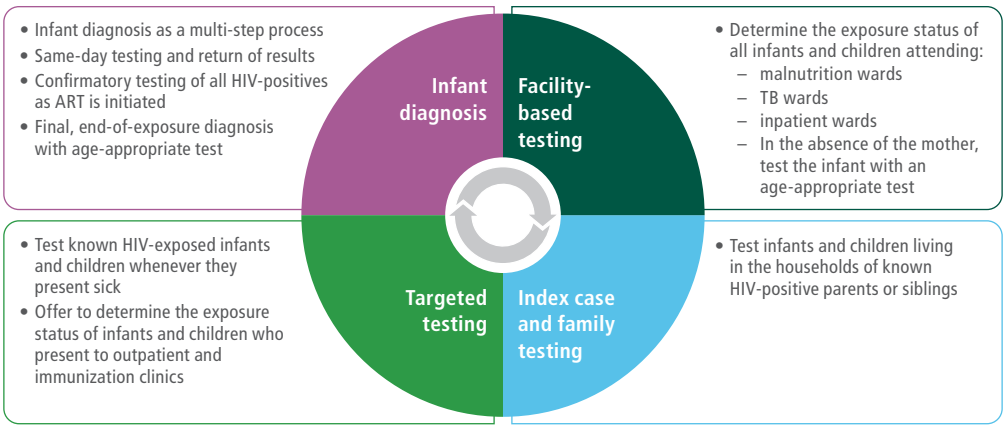
When resolving discrepant results, if A1 and Repeat A1 are both TP (syphilis) nonreactive results, report syphilis-negative.

2.8 HIV diagnosis among infants and children

Background

Because mortality in the first year of life is very high among untreated infants living with HIV, early HIV testing, prompt return of results and rapid initiation of treatment are essential *(30,31)*. HIV infection among infants can only be definitively confirmed with virological testing using NAT technologies. This is because maternal HIV antibody transmitted across the placenta may persist in the child up to 18 months of age, preventing the use of serological testing to diagnose HIV infection *(32,33)*. Access to early infant diagnosis has improved significantly in recent years, but only about 60% of all HIV-exposed infants were tested by the second month of age in 2020 *(19)*. For infants who are tested, delays in obtaining results and further losses in the testing-to-treatment cascade still occur *(34)* so that only 30% *(35)* of perinatally infected infants are effectively linked to services and start ART in a timely manner. Innovative approaches such as using assays at the point of care and adding a NAT at or around birth (0–2 days) can improve rapid identification and treatment initiation among infants *(4,36,37)*.

Fig. 2.6 Comprehensive HIV testing approach for infants and children



Although early infant diagnosis is critical to minimize early mortality, other opportunities for testing are also essential to capture infants and children living with HIV who are infected postnatally or who were missed by infant diagnosis services (Fig. 2.6). Ensuring timely diagnosis of HIV infection for children requires a mix of interventions provided at different times at different care points. For children older than 18 months of age, serological testing is used in the same manner as in adults following the nationally validated testing algorithm. Since children poorly utilize voluntary counselling and testing services, facility-based testing is essential to improve the identification of children living with HIV, especially those who are born to mothers who have not received interventions for preventing mother-to-child transmission *(3)*. Determining the exposure status of all infants and children who present to key entry points of health-care facilities, including malnutrition, TB and inpatient wards, and subsequently testing those identified as HIV exposed will support increased case-finding – each entry point has been observed to be a high-yield setting *(5)*. Implementing index-case testing (also called family-based testing) has led to remarkable improvement in identifying children missed by infant diagnosis programmes *(38)*, but more efforts are needed to widely scale up this intervention. Finally, targeted testing with the support of tools to increase the efficiency of testing at facilities at which low prevalence might not merit routine approaches is increasingly considered to manage competing priorities and limited resources at the facility *(39)*.

2.8.1 Timing of virological testing

Recommendation (2016)

The addition of nucleic acid testing (NAT) at birth to existing early infant diagnosis testing approaches can be considered to identify HIV infection in HIV-exposed infants *(conditional recommendation, low-certainty evidence)*.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3).*

Background

Infants who have HIV detectable by NAT at birth are likely infected prenatally, will progress to disease rapidly and, in the absence of treatment, experience high mortality in the first few months of life *(40,41)*. Infants infected at or around delivery may not have virus detectable by NAT for several days to weeks. The ability of NAT to detect virus in the blood may be affected by ARV drugs taken by the mother or infant for postnatal prophylaxis, resulting in false-negative results. This includes drugs present in the breast-milk as a result of maternal ART during breastfeeding. In addition, since HIV prevalence in the population decreases as a result of effective interventions to prevent mother-to-child transmission, the proportion of false-positive NAT results increases, underscoring the need to effectively confirm those identified as positive *(42,43)*.

Finally, the ongoing risk of acquiring HIV during breastfeeding can delay the final determination of HIV status beyond 18 months. For all these reasons, identifying the optimal timing and frequency of infant testing is very challenging. Existing testing approaches have attempted to enhance programmatic simplicity and maximize the uptake of testing by aligning the timing of testing with the childhood immunization schedule. However, given the recent decline in the prices of assays and the expansion of infant diagnosis programmes, alternative testing approaches can be considered that maximize uptake, retention and timely treatment initiation while responding to changing epidemic and transmission dynamics.

The complexity of infant diagnosis is now growing because of significant scale-up of "treat all" (including pregnant and breastfeeding women), implementation of enhanced postnatal prophylaxis, reduced mother-to-child transmission rates and the increased relative contribution of postnatal transmission. Infant diagnosis can no longer be considered primarily a one-test process, since it now requires additional testing over the duration of exposure. Accordingly, several additional key considerations will be necessary to strengthen the infant testing cascade through the entire exposure period. This includes ensuring that ART initiation is not delayed for the infants found to be living with HIV.

Rationale and supporting evidence

The optimal timing of virological testing to diagnose HIV infection among infants is determined by four factors: (1) when infection occurs (prenatally, intrapartum or postpartum during breastfeeding); (2) the sensitivity and specificity and predictive values of the assay being used; (3) the mortality risk by age and (4) retention in the testing and treatment cascade *(4)*. Relevant evidence that informed this recommendation includes survival curves, available data on the testing-to-treatment cascade and a recent diagnostic accuracy review on the performance of NAT at birth (0–2 days) and at four to six weeks of age in the context of exposure to ARV drugs *(44)*.

Although concerns have been raised about the potential delay of HIV detection as a result of ARV drug exposure *(42,43)*, no direct evidence currently confirms that the performance of NAT on dried blood spots at four to six weeks of age is lower in the context of ARV drug exposure (pooled sensitivity and specificity were 100% and 99.03% [95% CI 98.19–99.88%]). However, the quality of the available evidence is low, and more data on the performance of virological testing is urgently needed, especially in the context of maternal ARV drug exposure and enhanced (prolonged and multidrug) infant postnatal prophylaxis. Given the available evidence, the ability to detect both prenatal and intrapartum infections and to remain aligned with the provision of routine maternal and child health services such as scheduled immunization visits and co-trimoxazole prophylaxis, the age of four to six weeks remains the critical point at which to provide virological testing, as recommended in existing testing strategies *(16)*.

The accuracy of diagnostic tests was reviewed in 2015 *(44)* to consider adding NAT at birth to detect perinatal HIV infection. Two studies were identified with overall sensitivity of 67.8% [95% CI 60.9–74.8%] and specificity of 99.73% [95% CI 99.4–100%], reflecting the difficulty of detecting intrapartum infections. Because of relatively poor sensitivity emerging from the currently available evidence, a single NAT at birth is likely to miss many infections and should only be considered as an additional opportunity for testing rather as substituting for the existing approach of testing at four to six weeks of age.

Overall, the empirical evidence was insufficient to recommend universally including NAT at or around birth (0–2 days) as a way to improve infant and programme outcomes. Nevertheless, this approach has potential benefits since it provides an additional opportunity for testing and enables earlier identification of infected infants in the context of poor scale-up of infant diagnosis. Linking birth testing to prompt ART initiation and care has the potential to reduce the early mortality and morbidity observed among infants who are infected prenatally and for whom the disease progresses more rapidly. From a programmatic perspective, there are potential advantages (but a lack of experience) with adding NAT at birth (0–2 days) and uncertainty around the clinical benefits and potential difficulties of treatment from birth as well as the potential complexity and cost of adding an additional test at a new service delivery point. There are also challenges associated with starting treatment among newborns and preterm infants given the available ARV drugs for this age group (see subsection 4.3).

In 2015, focus group discussions *(45)* with 105 women living with HIV from Kenya, Namibia and Nigeria suggested that earlier infant testing could be acceptable since mothers are motivated to avoid disease progression among infants. However, there were also concerns about the potential lack of understanding about the need to retest infants with negative NAT results and the associated loss to follow-up as well as potential emotional overload for women immediately after giving birth and the challenge of preserving confidentiality in the presence of family, partners and others in labour wards. Overall, women in the focus groups showed some reluctance to accept routine virological testing at birth and more favoured having a range of options from which to choose.

Model-based analysis *(46)* undertaken in 2015 supported optimizing six-week testing before adding NAT at birth. In addition, it suggested that, under the ideal scenario of full uptake and retention (100% of HIV-exposed infants being tested and retained in the testing-to-treatment cascade), a two-NAT strategy, with the first test at birth and the second test after six weeks of age, improves survival compared with a single test at six weeks. Any testing programme, whether at birth or six weeks, must have a mechanism to return test results promptly and link infants living with HIV to care and ART. Based on programmatic, clinical and cost data from South Africa over the lifetime of HIV-exposed infants, the modelling found that a programme of birth and six-week testing could be very cost-effective in settings similar to South Africa. The model confirmed that false-positive results may be common (about 30 positive results of 100 may be false-positive), even with relatively high assay specificity (98.0–99.0%), especially if the risk of mother-to-child transmission is low (less than 2% at six weeks). Confirmatory

testing is critical to minimize toxicity, stigma and costs for uninfected infants with false-positive results.

Given the risks, benefits, possible acceptability and potential cost–effectiveness, the 2016 WHO consolidated HIV guidelines *(3)* recommended that adding NAT at or around birth (0–2 days) can be considered where feasible but only in parallel with efforts to strengthen and expand existing infant testing approaches. Existing recommendations that infants with an initial positive virological test result should start ART without delay remain important. Nevertheless, a second specimen should be collected to confirm the initial positive virological test result. Immediate initiation of ART saves lives and should not be delayed pending the results of the confirmatory test.

Implementation considerations

As infant diagnosis programmes are further scaled up, every effort should be made to improve the uptake of NAT, strengthen retention along the testing-to-treatment cascade, ensure confirmation of NAT positive results with a second sample and ensure that infants who test negative by NAT are retained in care until a final diagnosis is made. If adding NAT at birth is being considered, effective linkage to maternal HIV screening at the time of delivery should be ensured and the following steps should be taken:

- collection of data on the performance and feasibility of birth testing during implementation;
- improvement of uptake and retention in the testing-to-treatment cascade;
- active tracking of infants with negative NAT at birth to ensure that they return at six weeks for retesting and co-trimoxazole initiation; and
- retesting of infants who test positive at birth with a second specimen as soon as possible, with ART being started immediately after the first positive test and stopped if the second specimen tests negative.

Several countries have already started implementing NAT at birth. Several implementation considerations can be summarized from these experiences *(24)*.

- Countries that are considering birth testing should critically review current performance and opportunities for strengthening their six-week and overall infant diagnosis programme and consider key indicators (such as PENTA1 immunization visit coverage and attended delivery rate), so that the potential gains provided by birth testing can be investigated more fully. For example, in settings where the attended delivery rate is much lower than PENTA1 immunization visit coverage (six weeks), the added value of birth testing as a means of expanding infant diagnosis may be limited.
- Pilot projects are a good way to start obtaining national experience on this innovative testing approach, but fully measuring the impact requires that programmes collect data on the feasibility and impact of birth testing and linkage to ART initiation.
- Targeted approaches that provide birth testing only for high-risk infants are expected to have a higher yield than routine birth testing. This approach may be potentially less resource intensive and present a lower burden for health-care workers.
- Active tracking of infants with negative NAT results at birth is critical to ensure that they return at six weeks to be retested and start co-trimoxazole; establishing unique patient identifiers or other innovative mechanisms (such as bar codes) to track babies can be considered.
- It is crucial that the turnaround time for reporting test results to health facilities and caregivers be rapid to optimize the benefit from NAT at birth. Same-day point-of-care assays should be used whenever possible.

- Birth testing is acceptable to mothers, but challenges arise from the increased human resources needed, the difficulty of collecting blood samples from newborns, the need to ensure sample collection outside standard working hours and deliver results, linkage to ART and the nature of the infant diagnosis system as a whole (stock-outs, referral mechanisms and delayed results).
- The key to effective implementation is to ensure that newborns who have been identified as HIV-infected are linked to treatment immediately and that age-appropriate formulations are available to start them on treatment.
- Good leadership and coordination are needed to oversee service provision, support supervision, mentorship and the quality improvement cycle.

Ensuring accurate interpretation of the nine-month test

The 2016 WHO consolidated HIV guidelines *(3)* recommend that rapid diagnostic tests be used to assess HIV exposure among infants younger than four months, and HIV exposure among infants 4–18 months old should be ascertained by testing the mother. When the mother cannot be tested, current guidelines emphasize the importance of not considering a negative rapid diagnostic test result from an infant 4–18 months old as a definitive test of exposure. Box 2.6 highlights implementation issues.

Based on the 2016 WHO consolidated HIV guidelines *(3)*, rapid diagnostic tests are serological assays that can also be used to exclude established infection among healthy, HIV-exposed infants nine months and older. However, changes in transmission dynamics and in policy and practice have complicated using rapid diagnostic tests for determining infection status. Substantial drug exposure for infants with implementation of the "treat all" policy for mothers and enhanced postnatal prophylaxis of HIV-exposed infants may have resulted in viral load reduction and delayed antibody development among infants living with HIV. Finally, the occurrence of maternal infection in late pregnancy or during the postnatal period may have caused a lack of passive HIV antibody transfer to the HIV-exposed infant. These factors increasingly jeopardize rapid diagnostic test accuracy at nine months of age as a means of correctly ruling out established infection among HIV-exposed infants. These concerns are supported by findings from Kenya and Uganda *(47,48)*, where 15–40% of children younger than two years and identified as HIV-infected had a positive NAT but negative rapid diagnostic test.

Box 2.6 Using rapid diagnostic tests: implementation considerations

- Priority should continue to be given to testing mothers at all entry points to determine exposure status for infants and children younger than 18 months.
- If the mother is absent or unable to be tested, the infant should have a rapid diagnostic test, but negative results for infants older than four months should not definitively exclude exposure, and follow-up testing is required.
- If the mother is absent or unable to be tested and the infant presents with signs and symptoms of HIV infection, perform a NAT.
- Perform a NAT following any positive rapid diagnostic test for the mother or the infant and perform a confirmatory NAT following any positive NAT result.

Rapid diagnostic testing at nine months was initially recommended in the 2010 WHO recommendations on the diagnosis of HIV infection in infants and children *(49)*, with the goal of targeting NAT for the HIV-exposed infants most likely to be infected (such as those with a positive rapid diagnostic test) as a cost-saving measure. However, because of declining mother-to-child transmission rates, increasing availability and lower costs of NAT, changing transmission and drug exposure dynamics and the fact that rapid diagnostic tests are less effective at determining the need for NAT testing, such a targeted approach may be less compelling. Further, the added programmatic complexity and potential for inappropriately interpreting test results have additional unintended consequences.

Given the challenges and data outlined above, replacing the rapid diagnostic test at nine months with NAT can now be considered to minimize the challenges of interpretation and simplifying the infant testing algorithm.

2.8.2 Infant diagnosis algorithm

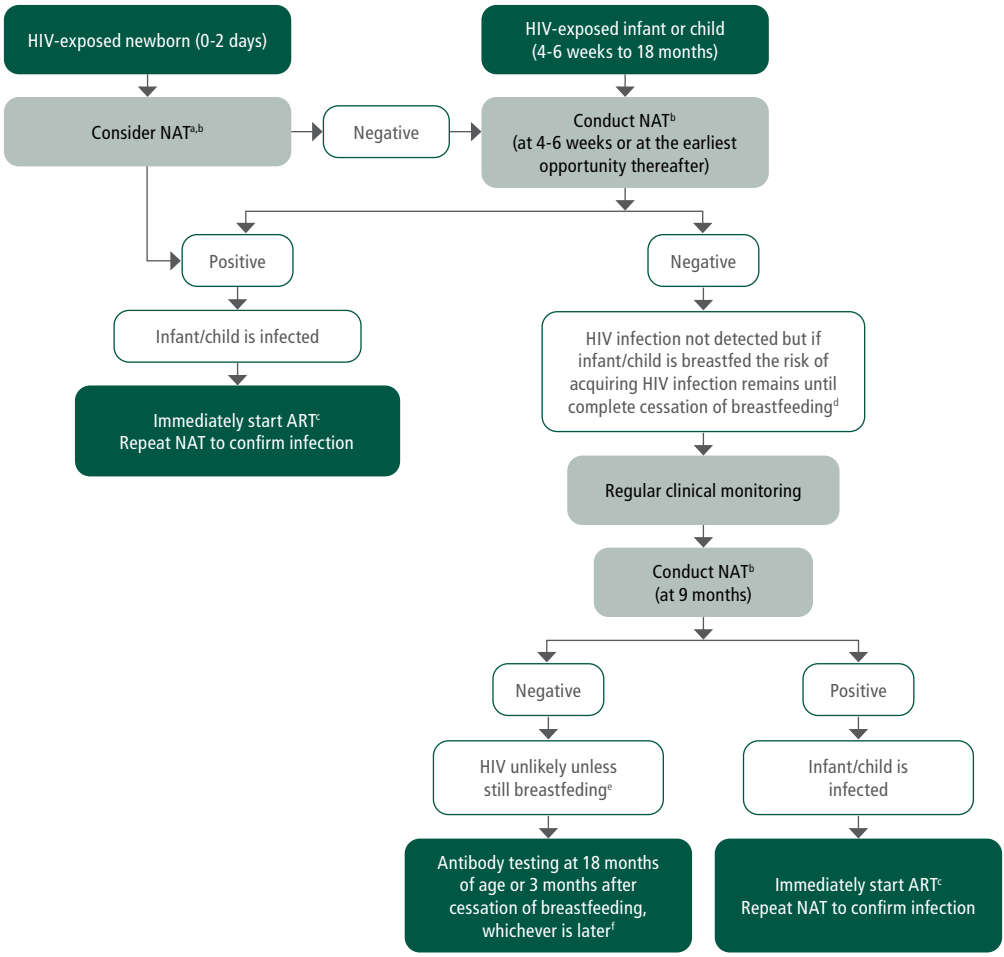
Infant diagnosis throughout the exposure period is critical to identify all possible infants and children living with HIV who need treatment. Several interventions, including recommendations on when to test, where to test and with what to test aim to improve case-finding and rapid linkage to treatment.

Several key considerations underscore the new simplified algorithm (Fig. 2.7):

- assessing HIV exposure status by performing a rapid diagnostic test on the mother;
- at nine months, performing NAT for HIV-exposed infants, symptomatic and asymptomatic, and even if previous NAT results have been negative;
- ensuring that indeterminate test results are repeat tested immediately and given priority for rapid resolution;
- ensuring that confirmatory testing is undertaken following any positive result; and
- ensuring that all HIV-exposed infants are regularly followed up until final diagnosis, including providing co-trimoxazole prophylaxis and clinical and nutritional assessment.

Finally, continuing infant retention in care remains critical until the end of the exposure period. More effort should be given to establishing a final diagnosis at 18 months of age or three months after breastfeeding ends, whichever occurs later. Although the coverage of the traditional six-week infant test is increasing and earlier time points are increasingly considered, the changing dynamics of transmission and increased drug exposure mean that increased efforts are needed to maintain follow-up throughout the entire exposure period. The aim is to ensure that all HIV-infected infants, including those infected in the postnatal period, are identified and receive treatment.

Fig. 2.7 Simplified infant diagnosis algorithm



[a] Based on *2016 WHO Consolidated ARV Guidelines (3)*, addition of NAT at birth to the existing testing algorithm can be considered.

[b] Point-of-care NAT can be used to diagnose HIV infection as well as to confirm positive results.

[c] Start ART without delay. At the same time, retest to confirm infection. As maternal treatment is scaled up and MTCT transmission rates decrease, false-positive results are expected to increase: retesting after a first positive NAT is hence important to avoid unnecessary treatment, particularly in settings with lower transmission rates. If the second test is negative, a third NAT should be performed before interrupting ART.

[d] For children who were never breastfed, additional testing following a negative NAT at 4–6 weeks is included in this algorithm to account for potential false-negative NAT results.

[e] The risk of HIV transmission remains as long as breastfeeding continues. If the 9-month test is conducted earlier than 3 months after cessation of breastfeeding, infection acquired in the last days of breastfeeding may be missed. Retesting at 18 months or 3 months after cessation of breastfeeding (whichever is later) should be carried out for final assessment of HIV status.

[f] If breastfeeding extends beyond 18 months, the final diagnosis of HIV status can only be assessed at the end of breastfeeding. If breastfeeding ends before 18 months, the final diagnosis of HIV status with antibody testing can only be assessed at 18 months. Antibody testing should be undertaken at least 3 months after cessation of breastfeeding (to allow for development of HIV antibodies). For infants younger than 18 months of age NAT should be performed to confirm infection. If the infant is older than 18 months, negative antibody testing confirms that the infant is uninfected; positive antibody testing confirms infant is infected.

Confirmatory testing of positive test results

A cost–effectiveness analysis undertaken to assess the value of confirmatory testing in different scenarios highlighted that confirmatory testing is indeed cost-effective *(50)*. Without confirmatory testing, this analysis showed that, in settings with mother-to-child transmission rates similar to those of South Africa, more than 10% of the infants initiating ART may in fact not be HIV-infected. Confirmatory testing of positive test results using a new sample, in accordance with WHO guidelines, may avoid this, although this policy is not consistently implemented (Box 2.7).

Programmes must ensure that all HIV-exposed infants are retained in care and tested appropriately throughout the entire exposure period, and all infants with a positive result should receive a confirmatory test. Further, those with repeatedly indeterminate test results should be actively tracked, retained and retested and their status should be resolved.

Box 2.7 Giving priority to confirmatory testing of positive and indeterminate tests

- Declining mother-to-child transmission rates globally have led to concerns about false-positive and indeterminate tests.
- People with indeterminate results need immediate repeat testing and should be managed according to the standard operating procedures (Fig. 2.8).
- People with repeated indeterminate results need a multidisciplinary team of health-care providers to support retention, tracking and status resolution.
- ART programmes need to give priority to confirmatory testing of all positive test results using a new sample.
- Clinical monitoring and further testing based on the national infant testing schedule need to be done until a definitive HIV status is established.

Finally, point-of-care infant testing is being implemented in several countries and settings (see subsection 2.8.3). Previously there was limited evidence on how to conduct confirmatory testing of positive point-of-care infant test results, but since the 2016 WHO consolidated HIV guidelines were published *(3)*, several studies have been published on its performance. Two point-of-care infant technologies are included on the WHO list of prequalified in vitro diagnostic products *(51)*. The results from both laboratory and field studies have shown performance comparable to that of laboratory-based technologies *(52)*. Further, two patient impact studies have been published that highlight the significantly improved patient outcomes when using point-of-care early infant diagnosis technologies *(53,54)*. Based on this updated evidence, point-of-care infant testing can be used to confirm positive test results.

2.8.3 Technologies to use for infant testing

Recommendation (2021)

Point-of-care nucleic acid testing should be used to diagnose HIV among infants and children younger than 18 months of age *(strong recommendation, high-certainty evidence)*.

Source: *Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (22).*

Background

Although significant recent investments in improving the diagnostic networks, centralized laboratories and sample collection networks have been made in most settings with a high burden of HIV infection, clear improvements in access to infant testing and treatment initiation of infants have not increased at the same rate. Substantial challenges and barriers remain. First, in 2019, only 60% of infants received an HIV NAT within the first two months of age *(19)*. Further, only 53% of children younger than 15 years living with HIV were receiving ART in 2019. The mortality of untreated, perinatally infected infants peaks at two to three months of age, with about 35% dying by 12 months of age and 52% by 24 months of age *(40,55)*. A recent systematic review of laboratory-based, standard-of-care infant testing found that the mean turnaround time from sample collection to the results received at the clinic was 4.5 days *(34)*. The time between the results received at the clinic to receipt by the caregiver was 4 days. The mean age at infant testing was 74 days; however, the mean age at treatment initiation was 214 days (seven months). In addition, in a subset of studies, 15% of the infants living with HIV had died between infant testing and ART initiation.

HIV NAT for infant diagnosis that can provide results on the same day of sample collection, similar to those used for older children and adult HIV testing, are now available on the market and have been approved by regulatory authorities *(51)*. Several of the device-based technologies available are multi-disease nucleic acid–based technologies that can be shared across diseases for other molecular assays. Additional device-free tests are being developed. In 2016, WHO conditionally recommended the use of point-of-care technologies for infant diagnosis *(3)*. This was based on low-certainty evidence from two diagnostic accuracy studies available at the time. Subsequent studies, including patient impact and clinical studies, have been completed and the guidance presented here was updated in early 2021 *(22)*.

Rationale and supporting evidence

Summary of review findings

A systematic review *(56)* of the clinical impact of using same-day point-of-care infant diagnosis compared with laboratory-based technologies identified seven studies *(53,54,57–61)* of more than 37 000 infants across 15 countries in sub-Saharan Africa. The studies included two randomized controlled trials and several large, well-characterized cohort studies. The studies directly evaluated similar outcomes, and only those that provided true point-of-care, same-day testing and results were included. The data and results were consistent across studies. Most studies had a low risk of bias for critical outcomes (including the time to receive results), except for retention in care and mortality outcomes, with the risk of bias noted to be serious given the limited number of studies and small sample sizes. The overall certainty of the evidence in this review was rated as high.

Median time from sample collection to delivering the result to the caregiver

Same-day point-of-care testing significantly reduced the time to deliver the result to caregivers (high-certainty evidence). Across all seven studies, the median time from sample collection to results received by the infants' caregivers was 0 days (95% CI 0–0 days) for point-of-care testing, regardless of the test used, the age of the infant or the type of health-care facility. Same-day results were returned 97% of the time when tested by point-of-care testing versus 0% for standard of care. For standard of care, the median time from sample collection to the caregiver receiving the result was 35 days (range 8–125 days, 95% CI 35–37 days). Five of seven studies had a median time to the caregiver receiving the result of more than 30 days. Six studies reported the median time from sample collection to initiating ART among infants testing positive for HIV was 0 days (95% CI 0–1) when tested using point-of-care testing *(2–6,8)*. When tested using point-of-care testing, 51% of infants living with HIV initiated ART on the same day as sample collection versus 0% when tested by the standard of care. For the standard of care, the median time from sample collection to treatment initiation was 40 days (range 6–127 days, 95% CI 34–43 days). The evidence was of high certainty overall.

Proportion of infants living with HIV initiating treatment within 60 days

The overall proportion of infants living with HIV initiating treatment within 60 days was 90% when tested at the point of care versus 54% when testing using the standard of care. The odds ratio of initiating treatment within 60 days was 7.9 (95% CI 5.4–11.5). The evidence overall was of high certainty.

Retention in care and mortality

Two studies provided follow-up data for infants living with HIV after diagnosis and initiating treatment *(53,59)*. The first study, from Mozambique, found that infants tested using point-of-care testing were significantly more likely to be retained in care after 90 days of follow-up compared with those receiving standard-of-care testing (adjusted rate ratio 1.40) *(53)*. The second study, from Zambia, found high mortality rates in both arms but no statistically significant difference in mortality or rates of viral suppression at 12 months of age; however, the sample size was small: only 20 of 81 infants living with HIV remained alive and in care at 12 months from both groups *(59)*. Overall, the evidence for these outcomes was of very low certainty.

The systematic review had several limitations. First, all studies were from sub-Saharan Africa, although this is consistent with the fact that more than 90% of HIV vertical transmission is in the WHO African Region. Although most studies had a low risk of bias for retention in care and mortality outcomes, the risk of bias and imprecision were noted to be serious given the limited number of studies and small sample sizes. The hub-and-spoke and near point-of-care concepts could not be analysed with the data available. In some studies, the hub-and-spoke results were provided within the same-day point-of-care arm and thus excluded because of inability to differentiate same-day versus near point-of-care testing. Although data suggest that same-day testing improves the return of results and treatment initiation, additional studies comparing same-day point-of-care with near point-of-care (less than seven days) and the standard of care (laboratory-based testing) testing would provide a more reliable basis for assessing this outcome.

Costs and cost–effectiveness

A synthesis of available cost–effectiveness models was developed using four cost–effectiveness studies and two overarching modelling approaches *(62)*. Johns Hopkins' model focused on sub-Saharan Africa and Zambia *(63,64)*; and the Cost–effectiveness of Preventing AIDS Complications (CEPAC)-Paediatric model focused on Zimbabwe *(65,66)*. All studies reported that point-of-care testing was more cost-effective than the standard of care defined in each study. Health benefits were described in terms of life-years saved, additional people

initiating ART and deaths averted. In most scenarios, integrating or sharing platforms across diseases (Xpert® TB testing or HIV viral load testing) resulted in point-of-care testing being cost-saving compared with the standard of care. In Zambia, point-of-care testing cost US$ 752 less than the standard of care per additional person initiating ART when the devices were shared across TB and HIV programmes.

Affordability

Current point-of-care infant diagnosis tests cost US$ 15–25 per test, with instruments costing about US$ 15 000.

Access to same-day point-of-care testing in four countries with a high burden of HIV (Malawi, Mozambique, Uganda and Zambia) is currently estimated to already be 30–50%. The estimated incremental cost to support access to 70%, 80% or 90% of HIV-exposed infants with point-of-care technologies would be US$ 60, US$ 109 and US$ 194, respectively *(67)*. These costs, for both point-of-care and laboratory-based testing, could be amortized across (but were not calculated within) other programmes, such as TB programmes, that may also use the devices. The remaining proportion of HIV-exposed infants would require access to infant testing through referral to laboratory-based devices.

Implementing point-of-care testing in these four countries would result in considerably more infants living with HIV initiating ART. With 70%, 80% or 90% point-of-care implementation for infant testing, 149 000, 162 000 or 175 000 infants living with HIV, respectively, would initiate treatment versus just 110 000 if the current rates of point-of-care testing were maintained. This would result in a cost of between US$ 325 and US$ 622 per additional person initiating ART.

Ethically, concerns about costs should not be a barrier to adoption. If the clinical and public health evidence in its favour is as conclusive as it seems, then the global health community must work with national governments and local authorities to supply point-of-care testing for infants. Paths forward would include appealing to international agencies and directly to the companies that build these diagnostics to lower their costs as much as possible.

Values and preferences

In a study from Kenya (74 interviews and six focus group discussions) and Zimbabwe (85 interviews and eight focus group discussions) of community members and elders, data were collected before point-of-care testing was introduced and after it had been in use for at least three months *(68)*. Reduced time to receive test results lowered caregiver anxiety about the child's HIV status and enabled families to start treatment earlier. Some considered printed point-of-care results more trustworthy than conventional handwritten results, believing that this reduced the chance of human error; a few distrusted HIV results that were generated too quickly. Caregivers were supportive of receiving point-of-care infant testing; however, additional collaboration with community groups is needed to increase acceptance and demand.

In addition, an online survey was undertaken among 43 people living with HIV to determine their values and preferences for using point-of-care testing for infant diagnosis compared with laboratory-based testing *(22)*. Most people living with HIV (72%) thought that collecting the sample, testing and providing the result within one hour would be acceptable. Half (51%) the respondents thought that knowing the HIV status as soon as possible would be worthwhile, and 41% thought that the benefit of same-day testing and results was that treatment could start immediately. The majority (81%) thought that testing, diagnosing and starting treatment for an infant on the same day was acceptable. Most people living with HIV (74%) thought that nurses would be able to test an infant for HIV and provide the test results at the same visit. Most respondents (72%) felt confident that health-care workers could do this.

Acceptability and feasibility

A study across eight African countries (Cameroon, Côte d'Ivoire, Eswatini, Kenya, Lesotho, Mozambique, Rwanda and Zimbabwe) comprised structured interviews with health-care workers providing infant testing services and semistructured interviews with national and regional laboratory managers or early infant diagnosis programme managers – before and after point-of-care infant testing was implemented *(69)*. Health-care workers found point-of-care infant testing easy to use (74% said it was very simple to run the test) and were very satisfied with the rapid turnaround time and ability to initiate treatment for infants living with HIV sooner (93%). All health-care workers recommended that the country increase point-of-care infant testing, while 87% would want a device in their health-care facility. Laboratory managers also supported scaling up point-of-care testing, although they were cautious about the need for reliable infrastructure to operate platforms.

In addition, an online survey was provided to 51 health-care workers and 53 programme managers to determine the acceptability and feasibility of implementing point-of-care infant testing *(22)*.

Survey of 51 health-care workers

Most (88%) felt comfortable running the test, delivering the result, counselling and starting treatment on the same day. Most health-care workers thought it would be acceptable (77%) and 65% prefer point-of-care infant testing, if available. The majority (88%) thought that the mother would accept same-day infant testing and in some cases positive diagnoses. Almost half (45%) of the health-care workers thought that implementing point-of-care infant testing would increase the workload in the clinic but that enough human resources were in place to implement it.

Survey of 53 programme managers

Most countries (72%) surveyed already have a policy for point-of-care infant testing; however, 85% indicated that most infant tests were done using standard-of-care laboratory-based testing. The majority (55%) thought point-of-care infant testing was preferable and feasible. More than half the programme managers (55%) did not think that the workload would increase if point-of-care infant testing was implemented either in the laboratory or in the clinic.

Diagnostic accuracy

A systematic review was prepared to provide summary estimates of the diagnostic accuracy of technologies capable of being used at the point of care. The performance overall was greater than 98% sensitivity and 99% specificity *(70)*.

Feasibility

Several technologies are on the market and available for use at the point of care; two already have WHO prequalification *(58)*. Many such devices have already been procured and are used for TB testing (Cepheid GeneXpert®) or infant diagnosis already (Abbott m-Pima™ and/or Cepheid GeneXpert®). Both tests use whole blood and do not require any additional equipment or expertise. The Abbott m-PIMA™ device can run about 6–8 tests per day, and the Cepheid GeneXpert® device can perform about 6–8 tests per module per day *(71)*. Across 140 developing countries with a high burden of TB and HIV infection (Cepheid's High Burden Developing Country programme), more than 11 600 devices have been delivered, comprising 52 000 modules. Nearly 12 million GeneXpert® TB cartridges were procured per year in 2017 and 2018; however, only 1.2 tests per module per day are currently being run. This leaves available capacity for expanding TB testing and considering HIV infant testing. Infant diagnosis should remain a priority when technologies are multi-purposed or shared across programmes.

Point-of-care technologies may not need to be procured for every health-care facility to reach most HIV-exposed infants. In most countries with a high burden of HIV infection, most HIV-exposed infants attend a small proportion of available health-care facilities. In an analysis from Malawi, Mozambique, Uganda and Zambia, 80% of HIV-exposed infants attended 32%, 33%, 12% and 10% of health-care facilities, respectively, indicating that modest procurement and focused placement of point-of-care technologies would affect many of the HIV-exposed infants *(67)*. Further, 10% of health-care facilities in each country serve 49%, 46%, 75% and 80% of HIV-exposed infants, respectively, in these four countries.

Equity

Ethical and equity considerations were developed to guide the guideline discussions *(72)*. Some of the conclusions found were the fair distribution of benefits and burdens at the population level (social justice), treating people as equally important (equity) and that infants should not be differentially disadvantaged relative to others in their communities when there is little to no risk of precluding the provision of other or ongoing health resources. If the rest of the community is not harmed from going without a specific resource by introducing point-of-care testing, then it is unclear what could possibly count against introducing it.

Rationale for the decision

The Guideline Development Group formulated a strong recommendation favouring point-of-care NAT to diagnose HIV among infants and children younger than 18 months of age. This was based on their judgement of the overwhelming benefits of the intervention, including, but not limited to:

- more rapid testing and return of results to caregivers and clinicians;
- increased retention in the testing-to-treatment cascade;
- fewer health facility visits for caregivers to receive results and more reliability in the timing of results and possibly more likelihood for test documentation;
- increased equity with adult HIV testing – same-day testing and receiving the result;
- increased access to ART and faster initiation, which may reduce mortality; and
- improved quality of services.

No major notable harm was identified. However, some considerations were noted around the general higher costs of testing (this was not viewed as a barrier to implementation), the more extensive network support required by health-care workers and the need for greater technical support and maintenance (service and maintenance, quality assurance and supply chain).

Implementation considerations

The Guideline Development Group highlighted several implementation considerations. First, point-of-care infant diagnosis technologies should be considered and used within the current infant diagnosis algorithm at any point when an NAT is required *(24)* (Fig 2.7). Second, access to high-quality diagnostic testing should be continually expanded across HIV and other molecular testing needs, ideally combining laboratory-based and point-of-care technologies in an integrated diagnostic network. If point-of-care testing cannot be done, alternative options must be found, including ensuring rapid laboratory-based testing. Optimal placement of point-of-care technologies should be considered within the context of the overall health system, including other disease programmes and needs. This will create efficiency and support expansion and improved diagnostic services for HIV and other diseases.

Finally, ensuring adequate human resources, training (including technical, result interpretation, counselling and supply chain), service and maintenance and quality assurance should be carefully considered. Clear messaging, communication and literacy considerations should be implemented to support demand generation, scale-up, trust and utilization, including close collaboration with community groups. Maximizing the clinical impact of point-of-care testing requires ongoing strengthening of treatment and care services for neonates, infants and children, same-day linkage of infants to treatment and care, reliable procurement of appropriate formulations for children and supported supervision for health-care workers managing these young infants.

Research gaps

Although substantial evidence was available to review this question, further implementation research on quality assurance approaches could be considered to understand the sustainable delivery of point-of-care testing for infant diagnosis. Further, a potential dual-claim point-of-care test should be investigated that can be used across infants, children and adults, both for HIV diagnosis and viral load to streamline supply chain and create more efficient diagnostic systems.

In addition, tests are being developed that may be device-free and closer to a traditional rapid diagnostic test. These will likely support further decentralization and require no capital investment for health-care facilities, especially those with low volumes. Diagnostic accuracy and clinical impact studies for these tests would be beneficial.

2.8.4 Rapid diagnostic tests for HIV serology

Recommendation (2016 and 2018)

- **Rapid diagnostic tests for HIV serology can be used to assess HIV exposure among infants younger than four months of age. HIV-exposure status among infants and children four to 18 months of age should therefore be ascertained by undertaking HIV serological testing in the mother** *(conditional recommendation, low-certainty evidence)*.
- **Rapid diagnostic tests for HIV serology can be used to diagnose HIV infection among children older than 18 months following the national testing strategy** *(strong recommendation, moderate-certainty evidence)*.

Sources: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3) and HIV diagnosis and ARV use in HIV-exposed infants: a programmatic update (24)*

HIV antibody assays reliably detect HIV antibodies among children but cannot distinguish persisting maternal HIV antibody from antibodies produced by the child. A positive HIV antibody test among infants and children younger than 18 months of age therefore confirms exposure to HIV but cannot definitively diagnose infection. In contrast, the presence of HIV antibodies is a quick and reliable means of definitively diagnosing HIV infection among children older than 18 months because maternal HIV antibodies are usually no longer detectable. Children who start ART as early as three to six months of age are unlikely to develop antibody response to the virus and may falsely test HIV-negative using a serological assay. Antibody testing should therefore not be used to confirm or rule out infection among children who are already receiving ART *(73–75)*.

Rapid diagnostic tests with performance comparable to that of traditional laboratory-based serological assays are commercially available. WHO guidelines recommend the use of HIV antibody testing with a minimum sensitivity of 99% and minimum specificity of 98% *(3)*. These assays may be particularly appropriate for use in resource-limited settings since they can be performed in clinic or community settings with minimal infrastructure. However, some concerns exist about the performance of rapid diagnostic tests, especially their ability to determine exposure and effectively exclude HIV infection at different ages *(49)*.

Assessing HIV exposure for infants and children younger than 18 months

A diagnostic test accuracy review was conducted to explore the performance of rapid diagnostic tests as serological assays to assess HIV exposure and HIV diagnosis at different points in time *(76)*. The four studies identified showed that the diagnostic accuracy of current commercially available rapid diagnostic tests corresponded closely with the reference standard (enzyme-linked immunosorbent assay (ELISA)) among infants aged zero to three months, when maternal antibody is detectable, with an average sensitivity of 95.4% (95% CI 89.3–98.1%) and an average specificity of 99.7% (95% CI 92.2–100.0%). Rapid diagnostic test performance after four months was lower, with average sensitivity for identifying HIV exposure dropping to 51.9% (95% CI 40.9–62.8%), likely resulting from waning maternal antibodies.

Although rapid diagnostic tests have significant potential to increasing access to and uptake of HIV testing, including in rural and remote areas, the available evidence suggests a potentially high risk that these tests will not capture HIV-exposed infants older than four months of age. Testing mothers is the best way to ascertain exposure and should be given priority whenever possible. When mothers cannot be tested, rapid diagnostic tests can be used reliably to ascertain HIV exposure among infants younger than four months of age. By contrast, when rapid diagnostic tests are used among infants and children four to 18 months of age, a negative result should not be considered as definitively excluding HIV exposure. If a child younger than 18 months is sick and the mother is not available for exposure to be assessed, a NAT should be performed regardless of the rapid diagnostic test result (Table 2.1).

HIV diagnosis among children older than 18 months

Five relevant studies showed that diagnostic accuracy among children older than 18 months using currently commercially available assays met existing WHO predefined standards for serology with an average sensitivity of 97.6% (95% CI 89.7–99.5%) and average specificity of 99.1% (95% CI 97.7–99.7%) *(77)*. The risk of false-negative or false-positive results is likely to be limited and outweighed by the potential increase in uptake of testing, especially when following the national validated testing algorithms used for adults.

Implementation considerations for using rapid diagnostic tests among infants and children

Overall, using rapid diagnostic tests for infants and children will support making HIV testing available in rural and remote areas. Although the cost implications have not been formally assessed, rapid diagnostic tests are less expensive than serology laboratory-based assays (considering the total cost of testing rather than the cost of the tests alone) and likely to be cost-effective, as suggested by similar analyses conducted in the adult population *(78)* and on the use of rapid diagnostic tests to screen for syphilis and malaria *(79–81)*.

Table 2.1 Use of rapid diagnostic tests for HIV serology based on age, exposure status and breastfeeding practice

Age group	Known HIV-exposed	Unknown HIV exposure status and breastfeeding	Unknown HIV exposure status and not breastfeeding[a]
0–4 months	Not useful since exposure is known and a rapid diagnostic test cannot determine infection status	**Test the mother** If the mother is not available, rapid diagnostic test for the child can reliably assess exposure	**Test the mother** If the mother is not available, rapid diagnostic test for the child reliably determines exposure
5–18 months	Not useful since exposure is known and a rapid diagnostic test cannot determine infection status	**Test the mother** If the mother is not available, a positive rapid diagnostic test establishes exposure, but a negative rapid diagnostic test does not rule out potential exposure. If the child is sick and the rapid diagnostic test is negative, perform NAT to assess HIV infection status.[b] Infants with a positive rapid diagnostic test result require NAT to diagnose infection.	**Test the mother** If the mother is not available, a positive rapid diagnostic test establishes exposure, but a negative rapid diagnostic test does not rule out potential exposure. If the child is sick and the rapid diagnostic test is negative, perform NAT to assess HIV infection status.[b] Infants with a positive rapid diagnostic test result require NAT to diagnose infection.
>18 months	Serological testing (including rapid diagnostic test) is recommended to assess HIV infection status unless the child is still breastfed. If the child is still breastfed, NAT should be provided three months after breastfeeding ends.		

[a]Not breastfed for at least 12 weeks before testing.

[b]Consider initiating ART for presumed HIV infection if highly suspected while waiting for the NAT results, especially if the rapid diagnostic test is positive.

Implementation considerations

Although the guidance for active case finding and facility-based testing and counselling among children has been in place since 2007, uptake of this recommendation has been poor. Issues around the legal age of consent and provider discomfort with disclosure have contributed to this lack of uptake, especially for adolescents and older children. A recent study in six primary clinics in Zimbabwe identified several other factors, including a perceived lack of importance attached to testing older children and a sense that testing was not warranted if children were asymptomatic *(10)*. Lack of time and reagents and discomfort with approaching male caregivers were also noted as reasons for not testing. In addition, a WHO survey of health-care workers, policy-makers and programme managers from 17 countries found that almost half the respondents felt that testing children in immunization clinics would either be easy or very easy

to do, suggesting that this policy is highly feasible to implement. Experience from countries that have been trying to roll out facility-based testing and counselling for children highlights the importance of thorough linkage to care and services for children who are exposed or infected. Linkage to care may be easier for children in inpatient settings than for those in busy outpatient clinics. The negative impact of HIV testing on the uptake of other essential childhood interventions, such as immunization, has been cited as an argument against integrating testing in immunization clinics *(11)*. A study in the United Republic of Tanzania showed that, although integration of HIV testing resulted in an increase in immunization rates in urban centres, there was a decrease in rural facilities, possibly reflecting higher levels of stigma in rural communities *(12)*.

2.8.6 Minimizing false-positive results by introducing an indeterminate range for infant diagnosis when using NAT

Recommendation (2018)

- **An indeterminate range[a] of viral copy equivalents should be used to improve the accuracy of all nucleic acid–based early infant diagnosis assays** *(strong recommendation, moderate-certainty evidence)*.

[a] Indeterminate range: a range of viral copy equivalents that would be too low to be accurately diagnosed as HIV infected. The indeterminate range suggested is currently estimated to be approximately equivalent to a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay.

Source: *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (25)*

Table 2.2 Indeterminate range cycle threshold equivalents of current nucleic acid infant diagnosis assays

Assay	Estimated indeterminate range cycle threshold
Abbott RealTi*m*e HIV-1 Qualitative	≥29
Abbott m-PIMA™ HIV-1/2 Detect	[a]
Cepheid Xpert® HIV-1 Qual	[a]
Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0	≥33
Roche COBAS® HIV-1 Quantitative nucleic acid test for use on the COBAS® 4800 System	≥38
Roche COBAS® HIV-1 Quantitative nucleic acid test for use on the COBAS® 6800/8800 Systems	≥37

[a] Due to the nature of the technology and associated simplified result reporting (point-of-care assay capable of decentralization and operation by non-laboratory staff), the supplier is working on revising the display of the results to incorporate the indeterminate range to indicate those specimens that require repeat testing, in accordance with WHO guidelines.

Background

In 2016, WHO recommended that HIV virological testing be used to diagnose HIV infection among infants and children younger than 18 months of age and that ART should be started without delay while a second specimen is collected to confirm the initial positive virological test result *(3)*. Confirmatory testing is critical because of the risk of false-positive results, potential contamination with maternal blood (and virus), specimen mislabelling or mix-up, laboratory or cross-sample contamination and an observed trend of low detection of HIV among both mothers and infants because of increased exposure to maternal treatment and enhanced prophylaxis *(82)*. The potential for false-positive results is of particular concern in settings in which the mother-to-child transmission rate is less than 5%, since the positive predictive value of highly sensitive nucleic acid–based technologies may decrease to nearly 70% *(83)*. However, in some countries in sub-Saharan Africa, less than 10% of infants with an initial positive test result receive a confirmatory test, potentially resulting in a significant proportion (12.5%) of infants starting lifelong treatment unnecessarily.

Although a variety of causes may result in a false-positive test result, most infants with false-positive test results have low levels of viraemia; however, guidance is limited on how to interpret low levels of viraemia detected in early infant diagnostic assays. Test results that the nucleic acid–based technology reports as detectable are generally considered to be positive, relying on the thresholds of detection provided by the manufacturers. To ensure that infants do not start lifelong treatment unnecessarily, various approaches have been considered. Guidelines in the United States of America suggest that infants should not be considered HIV-positive unless they have the equivalent of at least 5000 viral copies/mL *(84)*, and South Africa has introduced an indeterminate range that requires further testing before a definitive diagnosis is provided and treatment is initiated *(85)*.

Previous WHO guidelines do not specifically address this growing concern about false-positive test results. Further, there is currently no specific recommendation on what level of viraemia should be considered a true positive result among infants.

Supporting evidence

Systematic review

A systematic review of 32 studies using any indeterminate range found 14 753 non-negative test results, of which 2436 (16.5%, 95% CI 15.9–17.1%) were classified as indeterminate *(86)*. One study reporting the final diagnoses of indeterminate cases found that 76% of infants with an initial indeterminate test result were negative on retesting, suggesting that most infants were not HIV-infected despite the initial non-negative test result. These data indicate that, in countries not implementing an indeterminate range to manage early infant diagnosis test results, up to 12.5% of non-negative results could be falsely positive on initial testing, and those infants could potentially start lifelong treatment unnecessarily.

The optimal indeterminate range is considered to be the approximate equivalent of a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay. This represented a balance between the proportion of infants living with HIV that would be incorrectly identified as indeterminate (about 8–13%) and the proportion of HIV-uninfected infants that would potentially start treatment unnecessarily (about 2–7%). The cycle threshold values vary by the assay used and cannot be directly applied between technologies or assays. Because true-positive infants with low levels of viraemia generally have less rapid disease progression and need to be followed up until final diagnosis is ascertained, the Guideline Development Group determined that having a higher proportion of true-positives incorrectly classified as indeterminate than false-positives is more acceptable, since all indeterminate test results should be followed up and repeat tested as soon as possible before lifelong treatment is administered.

Implementing an indeterminate range will support more accurate nucleic acid–based early infant diagnosis. Fewer HIV-negative infants will probably start unnecessary lifelong treatment, since most false-positives will fall within the indeterminate range rather than being identified as positive. This will limit confusion and challenges in interpreting potential subsequent discordant test results if the infant was classified as positive and already initiated treatment. Finally, in addition to reducing unnecessary treatment by limiting false-positive results, an indeterminate range will promote increased attention to confirmatory testing of all non-negative test results and trigger corrective action to minimize potential contamination at the point of collection or in the laboratory. See Fig. 2.8.

Possible harm identified includes the potential requirement for additional specimens, which could result in delays to treatment initiation and the associated risk of loss to care for HIV-positive infants with indeterminate results on the first sample. However, infants with low levels of viraemia (the small proportion of HIV-positive infants who would fall within the indeterminate range) are expected to progress more slowly to morbidity and mortality *(87)*. Further, implementing an indeterminate range may reduce the confidence of health-care workers in early infant diagnosis testing programmes if high rates of resampling and retesting are required.

Cost and cost–effectiveness

Implementing an indeterminate range has been determined to save costs since minimum additional resources will be required to retest all non-negative specimens, especially those with an initial indeterminate test result, compared with the cost of unnecessary lifelong treatment.

A cost–effectiveness model compared the standard of care (no indeterminate range) to a variety of indeterminate range options and concluded that implementing an indeterminate range is far more effective than the standard of care across a variety of viral ranges *(88)*. Since the prevalence, positivity and mother-to-child transmission rate at each testing time point decrease, the cost–effectiveness of an indeterminate range increases and saves more costs than no indeterminate range.

Equity and acceptability

Implementing an indeterminate range may improve equity by ensuring that HIV-negative infants do not start lifelong treatment unnecessarily. This may also enable access to available treatment for other infants correctly identified as HIV-positive.

A survey of values and preferences that included people living with HIV, health-care workers and programme managers found an indeterminate range to be highly acceptable. Most respondents preferred that the meaning of an indeterminate test result be clearly explained to mothers and other caregivers. The primary concern for all groups was the potential for confusion arising from inadequate explanations about the need to resample and retest the infant. However, as long as clear guidance on the meaning of an indeterminate test result is provided to mothers and other caregivers, there will be no uncertainty about the acceptability of implementation.

Feasibility

Implementing an indeterminate range is expected to be feasible, especially if indeterminate test results are repeat tested using the same specimen. In the survey of programme managers, slightly more than half indicated that their country already has a written standard operating procedure for requesting a second specimen for invalid test results. However, there were some concerns regarding the additional time required for repeat testing all indeterminate test results and the need for storing specimens at the laboratory.

To ease the acceptability, feasibility and implementation of an indeterminate range, a standard operating procedure has been developed to support and guide countries based on expert opinion and values and preferences surveys *(24,89)*. This standard operating procedure suggests that all indeterminate tests be repeat tested on the same specimen, if and when available. Most indeterminate test results are expected to be resolved with a repeated test on the same specimen, which would alleviate the need for and delay incurred in requesting a new specimen from the infant *(82)*. If the same specimen cannot be repeat tested, then a new specimen should be requested and tested as quickly as possible. Repeat testing of the same sample may not be possible with point-of-care or near point-of-care technologies when the sample is directly applied from the heel to the cartridge; however, in such instances a new sample should be taken and immediately tested to confirm a positive test result.

This recommendation to use an indeterminate range to support more accurate diagnosis of infants should be implemented for any nucleic acid–based test performed for infants younger than 18 months, including testing at birth and at six weeks of age.

Implementation considerations

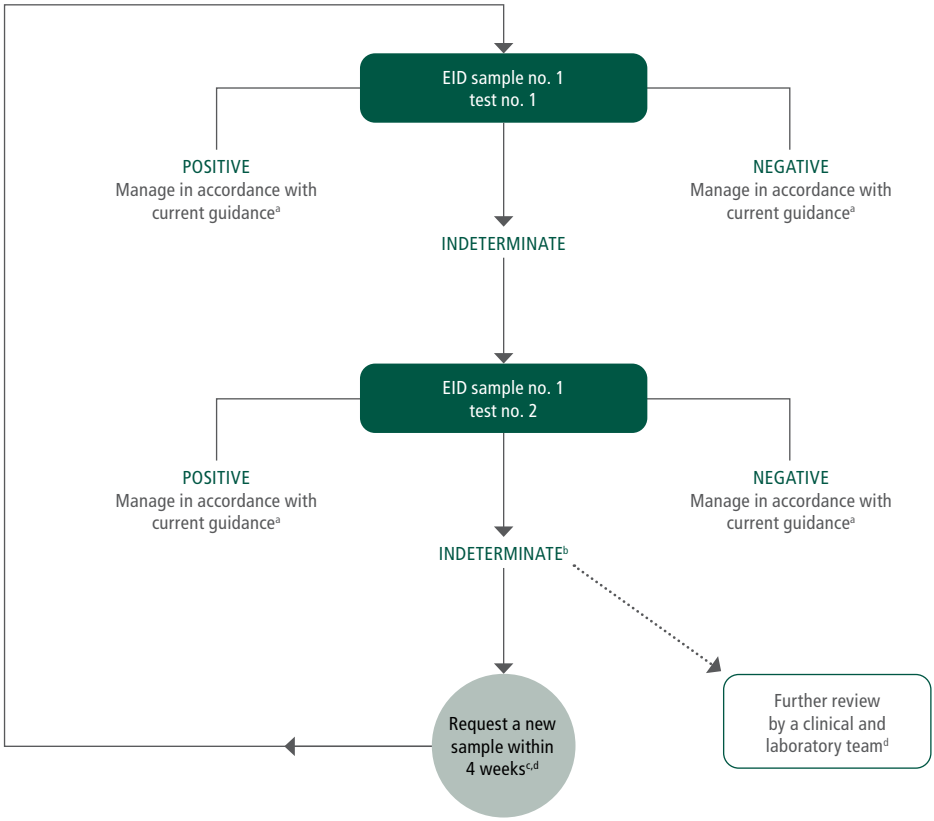
Generally, early infant diagnostic assays measure the presence of virus using real-time nucleic acid–based technologies that often report cycle thresholds. The cycle threshold – the polymerase chain reaction (PCR) cycle when amplification is observed – is inversely correlated with the amount of virus in a sample.

Based on the meta-analysis and cost–effectiveness modelling, the Guideline Development Group assessed that detecting an approximate equivalent of a cycle threshold of 33 on the Roche COBAS® Ampliprep/COBAS® TaqMan® HIV-1 Qualitative Test v2.0 assay would be the most appropriate value to balance the risks and benefits of introducing an indeterminate range. Note that the cycle threshold values vary by assay used and cannot be directly applied between technologies or assays. Further, additional consideration may be necessary for countries using plasma as a sample type for infant testing rather than whole blood or dried blood spots, since the latter sample types typically capture and amplify intracellular nucleic acids that may increase detected viral levels.

Research gaps

Research priorities regarding using an indeterminate range include the need for more detailed evidence on the impact of implementing an indeterminate range in populations with increased drug exposure and enhanced infant prophylaxis, the time of testing (earlier testing near birth), various sample types, differences in prevalence and different virus subtypes. More research would be valuable on the best messaging for health-care workers and mothers and other caregivers and on the optimal standard operating procedure for indeterminate test results. Further, understanding the feasibility of implementing an indeterminate range with all available nucleic acid–based technologies for early infant diagnosis and in various programmatic settings will be critical.

Fig. 2.8 Managing indeterminate test results: standard operating procedure



[a] Please refer to chapter 3 for further details on postnatal package of care.

[b] Do not report as positive or initiate ART but maintain prophylaxis in accordance with current guidance.

[c] Repeat samples should be given priority in the laboratory.

[d] A team of laboratories, clinicians, paediatricians, complex case experts (if possible) and caregivers should review repeated indeterminate results in two separate samples together with clinical information. Infants should be actively tracked to ensure follow-up and retention.

2.8.7 Managing discordant results and treatment interruption

Since 2010, WHO has recommended initiating infants on ART after an initial positive NAT, while simultaneously collecting a confirmatory sample. The 2016 WHO consolidated HIV guidelines *(3)* suggest that if the second (confirmatory) NAT is negative, a third NAT, either qualitative or quantitative (viral load), should be performed before considering interrupting ART. The introduction of an indeterminate range should potentially reduce the number and proportion of infants with discordant test results (different NAT results on separate samples); however, guidance on how to conduct treatment interruptions is needed.

Several factors should be considered when assessing people for ART interruption after discordant test results (positive then a negative result) are followed by a third test with a negative result:

- the infant ought to have no clinical signs or symptoms suggesting HIV infection *(49)*;
- a follow-up plan should be agreed on with the family, caregiver(s) and health-care staff; and
- tracking information (phone, address, etc.) of the family and caregiver(s) should be collected and confirmed.

The following factors should be considered when following up any infant undergoing treatment interruption.

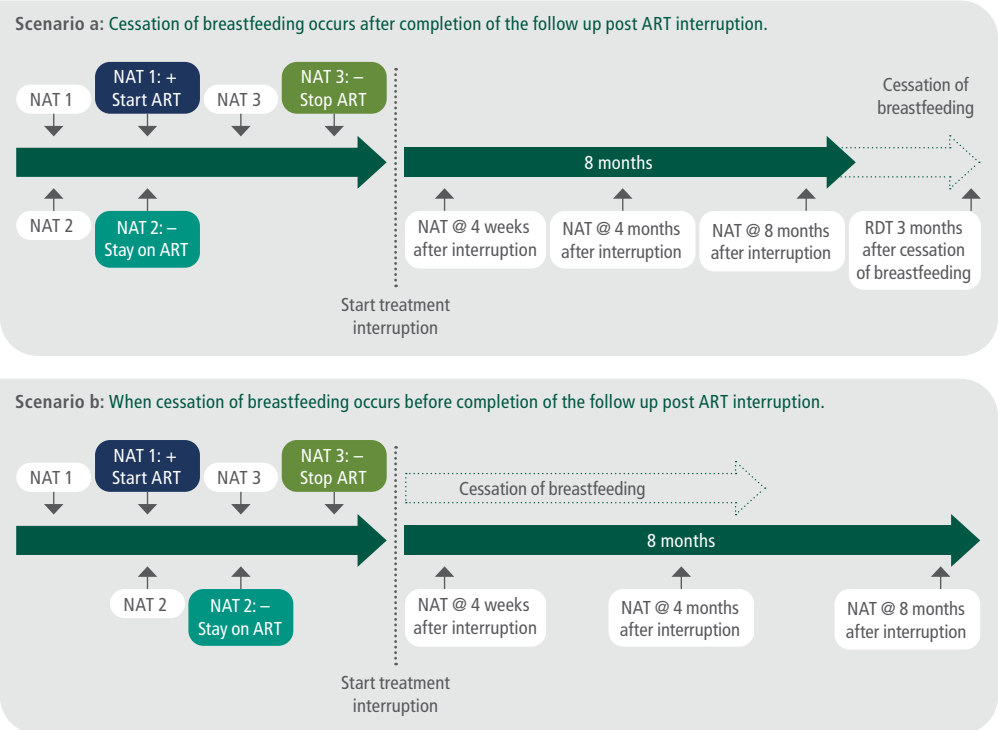
- Active follow-up is needed to ensure that a potentially infected infant is retained in care and reinitiates treatment if viral rebound occurs.
- Viral rebound among infants living with HIV starting treatment early is expected to happen within eight months of interruption in >99% of cases *(90)*.
- Infants who develop signs and symptoms indicating HIV infection should undergo immediate testing.
- Breastfeeding and continued risk of transmission require follow-up and appropriate testing throughout the period of risk until final diagnosis.
- There is value in minimizing follow-up testing by leveraging existing opportunities for infant testing (based on the national infant testing schedule and immunization or well-child appointment schedules) until final diagnosis is ascertained.

Few countries have existing policies on how to interrupt treatment among infants with discordant test results. South Africa, for one, has implemented policies with intensive laboratory and clinical follow-up of these infants for 18 months *(85)*. Both early infant diagnosis (qualitative) and viral load (quantitative) tests are performed at four weeks and three months and every three months after treatment interruption. However, since the likelihood of these infants being HIV-infected is low, a less aggressive eight-month approach is also reasonable to simplify the follow-up procedure: this is supported by emerging evidence on the timing of viral rebound among infants living with HIV treated early *(55)*. In this case, both early infant diagnosis (qualitative) and viral load (quantitative) tests could be performed at four weeks, four months and eight months after treatment interruption (Fig. 2.9). Infants who test positive on any follow-up test in either protocol should reinitiate treatment in accordance with current guidelines *(3)*, and a confirmatory sample should be taken.

Any standard operating procedures for interruption should be implemented considering the continuous risk of transmission resulting from breastfeeding and, once the intensive follow-up is completed (eight months after treatment interruption), the national infant testing schedule for HIV-exposed infants should be applied to ensure an appropriate final diagnosis. If breastfeeding has stopped before the end of the intensive follow-up, final HIV status can be defined with NAT performed at least six weeks after breastfeeding ends, as indicated in Fig. 2.9, scenario b.

Fig. 2.9 Managing discordant results and treatment interruption

Early infant diagnosis and viral load at 4 weeks, 4 months, and 8 months after interruption



Research gaps

Several critical research gaps need to be addressed to fully inform the implementation of infant testing strategies. The impact of maternal treatment and infant prophylaxis may need to be assessed as drug exposure increases and vertical transmission decreases. Further, determining and evaluating the most effective approaches to retaining infants throughout the exposure period until final diagnosis will be critical. Tracking tools can ensure effective tracking of infants throughout the exposure period and including those negative at previous testing time points.

More experience and data are needed to assess the impact of adding virological testing at birth on the successful initiation of newborn ART, infant outcomes and uptake of virological testing at six weeks. This would also include the added value of integrating birth testing with BCG vaccination. The feasibility and acceptability of virological testing at birth also need to be further explored in the context of national programmes at different prevalence settings and in different epidemic contexts as well as for high-risk infants only.

The frequency of testing during breastfeeding and weaning should be explored to enhance early diagnosis in this period. This should be complemented to include the optimal timing and frequency of viral load testing of pregnant and breastfeeding women.

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3. HIV PREVENTION

3.1 Combination HIV prevention

Combination prevention programmes use a mix of evidence-based biomedical, behavioural and structural interventions to meet the current HIV prevention needs of individuals and communities to have the greatest possible impact on reducing the number of people newly infected. Well-designed combination prevention programmes need to reflect the local HIV epidemiology and context. They should focus resources to reach populations at greatest HIV risk with effective, acceptable prevention to address both immediate risks and underlying vulnerability. Combination prevention mobilizes communities, civil society, the private sector, governments and global resources in a collective undertaking. It requires and benefits from enhanced partnership and coordination and should incorporate mechanisms for learning, capacity building and flexibility to permit continual improvement and adaptation to the changing epidemiological environment.

ARV drugs play a key role in HIV prevention. People taking ART who achieved viral suppression (<200 copies/mL) do not transmit HIV to sexual partners. ARV drugs taken by people without HIV as pre exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are both highly effective in preventing HIV acquisition.

Other biomedical interventions that reduce HIV risk practices and/or the probability of HIV transmission per contact event include the following.

- **Male and female condoms and condom-compatible lubricant.** Male condoms are estimated to reduce heterosexual transmission by at least 80% and to offer 64% protection in anal sex among men who have sex with men, if used consistently and correctly *(1,2)*. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect *(3)*.
- **Harm reduction for people who inject drugs.** This is provided through a range of interventions and services.
  - Needle and syringe programmes are highly effective in reducing HIV transmission through injecting drug use *(4)*.
  - Opioid substitution therapy with methadone or buprenorphine is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV transmission through injecting drug use. Opioid substitution therapy is also effective in improving ART uptake and adherence for people dependent on opioids *(5,6)*.
  - Overdose management with community distribution of naloxone to prevent opioid overdose death *(7)*.
  - WHO is developing new recommendations on behavioural interventions to reduce the risk of transmission of HIV, hepatitis and sexually transmitted infections through chemsex, which may include injecting drug use.

- **Voluntary medical male circumcision.** The 2020 WHO guideline on voluntary medical male circumcision recommends that the intervention should continue to be promoted as an additional efficacious HIV prevention option within combination prevention for adolescent boys aged 15 years and older and adult men in settings with generalized epidemics to reduce the risk of heterosexually acquired HIV infection. High-certainty evidence from three randomized controlled trials *(8)* is supported by observational studies conducted between 1986 and 2017, showing that voluntary medical male circumcision reduced the risk of heterosexual acquisition of HIV by about 60%. Other benefits of medical male circumcision include the reduced risk of some other sexually transmitted infections among women and men, including human papillomavirus, the cause of cervical cancer *(9)*.

In deciding whether to offer voluntary medical male circumcision to younger adolescents, ages 10–14 years old, safety, which is affected by their evolving physical development, and capacity to provide informed consent should be considered along with factors such as public health impact, the acceptability and feasibility of delivering voluntary medical male circumcision along with other services and maintaining the benefits of high voluntary medical male circumcision coverage *(8)*.

A minimum package of services, including safer sex education, condom promotion, the offer of HIV testing services and management of sexually transmitted infections, must be delivered along with the male circumcision procedure. Other health services, such as hypertension and/or TB screening, malaria management and tetanus toxoid-containing boosters could be added *(8)*.

Reaching men with HIV prevention, testing, treatment and care important is important for men's health and for preventing HIV among their sexual partners. Interventions are needed that address barriers to reach men and build on facilitators to enhance adult men's uptake of voluntary medical male circumcision and other health services. Evidence and case examples are available in the 2020 voluntary medical male circumcision guidance *(8)*, with new examples being updated with experience.

Embedding voluntary medical male circumcision service delivery within the overall health system is key to achieving sustainability and aligns with global efforts to strengthen health systems and achieve universal health coverage. The WHO health systems building blocks can serve as a framework to consider issues and opportunities for sustaining voluntary medical male circumcision services *(8)*.

Behavioural interventions can reduce the frequency of potential transmission events, including the following:

- **Targeted information and education.** These are programmes that use various communication approaches, such as school-based comprehensive sexuality education, peer counselling and community-level and interpersonal counselling (including brief interventions) to disseminate messages. These messages encourage people to reduce behaviour that may increase the risk of acquiring HIV and increase behaviour that is protective (such as safer drug use, delaying sexual debut, reducing the frequency of unprotected sex, using male and female condoms correctly and consistently and knowing your and your partner's HIV status). Recognition is growing that social media and mobile technology are important tools that can be integrated in HIV prevention programmes and can be particularly critical in informing about and providing prevention services to populations such as men who have sex with men.
- Enabling interventions to address structural barriers to accessing services may increase access to, uptake of and adherence to prevention as well as testing and treatment services. Such interventions address the critical social, legal, political and enabling environment that contribute to HIV transmission, including legal and policy reform towards decriminalizing behaviour (such as drug use, sex work and same-sex sex), measures to reduce stigma and

discrimination (including in the health sector), promoting gender equality and preventing gender-based violence and violence towards key populations, economic and social empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.

Combination prevention for key populations

WHO recommended a comprehensive package of evidence-based HIV-related interventions and services for all key populations in 2014, updated in 2016 *(10,11)*. The package comprised clinical interventions and a set of critical enablers required for successful implementation of programmes and access for the five key populations[3]. WHO is in the process of updating these guidelines to have a broader health focus and integrate HIV, hepatitis and sexually transmitted infections. The updated guidelines will recommend interventions and prevention packages by population, which will continue to include the critical enablers as outlined in Box 3.1.

Box 3.1 Essential strategies for an enabling environment

1. Supportive legislation, policy and financial commitment, including decriminalization of behaviour such as sex work, same-gender sex, gender identity and expression and drug use
2. Addressing stigma and discrimination, including by making health services available, accessible and acceptable
3. Community empowerment
4. Addressing violence against people from key populations

Source: *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (11).*

3.2 Pre-exposure prophylaxis for preventing the acquisition of HIV

PrEP is the use of ARV drugs by HIV-negative individuals to reduce the acquisition of HIV infection. Based on evidence from randomized trials, open-label extension studies and demonstration projects, WHO recommended daily oral PrEP containing tenofovir in 2015 as an additional prevention choice for people at substantial risk of HIV infection. In 2019, WHO updated this recommendation to include an additional dosing regimen, called event-driven PrEP, for cisgender men who have sex with men.

In 2021, WHO released a conditional recommendation that the dapivirine vaginal ring may be offered as an additional prevention choice for women[4] at substantial risk of HIV infection as part of combination prevention approaches *(12)*. As evidence for other PrEP products, including long-acting formulations, becomes available, WHO may make new or updated recommendations for PrEP.

[3] WHO defines key populations as men who have sex with men, people in prisons and other closed settings, people who inject drugs, sex workers and transgender people.

[4] For the recommendation on the dapivirine vaginal ring, the term women applies to cisgender women, meaning women assigned female at birth. There is no research at this time to support the dapivirine vaginal ring for other populations.

3.2.1 Oral pre-exposure prophylaxis for preventing the acquisition of HIV

Recommendations (2016)

Oral pre-exposure prophylaxis (PrEP) containing TDF should be offered as an additional prevention choice for people at substantial risk[a] of HIV infection as part of combination HIV prevention approaches *(strong recommendation, high certainty evidence)*.

[a] See Box 3.2 for reflections on the definition of substantial risk of HIV infection.

Source: *Guidelines: updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (12).*

Background

In the 2016 consolidated HIV guidelines, WHO recommended oral PrEP containing TDF as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches *(13)*, replacing previous recommendations *(10,14)*. This recommendation was based on a systematic review of 12 trials that addressed the effectiveness of oral PrEP and were conducted among serodiscordant couples, heterosexual men, women, men who have sex with men, people who inject drugs and transgender women *(15)*. The review showed that, where adherence was high, significant levels of efficacy were achieved, demonstrating the value of this intervention as part of combination prevention approaches.

By recommending PrEP for people at substantial risk (see Box 3.2), the offer of PrEP can be focused based on local epidemiology and individual assessment rather than solely on a risk group, enabling a wider range of populations to benefit and ensuring that implementation is informed by local information regarding the settings and circumstances of HIV transmission.

In 2017, WHO released the PrEP implementation tool *(16)* and a technical brief on preventing HIV during pregnancy and breastfeeding in the context of PrEP *(17)*. In 2018, WHO published a report on PrEP policy adoption by countries and an update on the interchangeability of FTC and 3TC in PrEP regimens *(18)*.

In 2019, WHO published a technical brief updating the WHO recommendation on oral PrEP to include the option of event-driven dosing for cisgender men who have sex with men *(19)*. This consists of the use of a double dose of oral PrEP 2–24 hours before sex, followed by a third dose 24 hours after the first two doses and a fourth dose 48 hours after the first two doses. This has been described as 2+1+1. If more sex acts take place in the following days, a single dose can be continued daily as long as sexual risk continues, with a single daily dose taken for each of two days after the last sex act. In 2019, WHO also published a technical brief on prevention and control of sexually transmitted infections in the era of oral PrEP for HIV *(20)*.

Since WHO released the recommendation on oral PrEP in 2015, more than 100 countries have incorporated PrEP into their national HIV guidelines, and PrEP users have been reported in 77 countries *(21)*.

Box 3.2 "Substantial risk of HIV acquisition"

When this recommendation was initially made in 2016, WHO defined substantial risk of HIV infection provisionally as HIV incidence greater than 3 per 100 person–years in the absence of PrEP. HIV incidence greater than 3 per 100 person–years has been identified among men who have sex with men, transgender women and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection. In 2016, it was suggested that implementing PrEP in a population with this level of HIV incidence was considered cost-effective or cost saving, although PrEP may still be cost-effective at lower HIV incidence levels.

However, individual risk varies considerably within populations depending on individual behaviour and the characteristics of sexual partners. In locations with a low overall incidence of HIV infection, there may be individuals at substantial risk who should be offered PrEP services *(22)*. PrEP programmes should consider local context and heterogeneity in risk. Individual characteristics and behaviour that could lead to exposure to HIV, rather than population-level HIV incidence, are most important when considering those who might benefit from PrEP.

Individuals requesting PrEP should be given priority to be offered PrEP, since requesting PrEP likely indicates there is a risk of acquiring HIV. Cost–effectiveness should not be the only consideration when implementing PrEP programmes, since remaining HIV negative and having control over HIV risk has intangible value to people and communities.

Rationale and supporting evidence

This section summarizes the rationale and supporting evidence for the recommendation on daily oral PrEP from the 2016 consolidated HIV guidelines. This was based on a systematic review of 12 randomized controlled trials on TDF-containing oral PrEP. These findings have been published in detail elsewhere *(15)*. A more recent systematic review had similar findings *(23)*.

Summary of review findings

A systematic review and meta-analysis of PrEP trials containing TDF demonstrated that PrEP is effective in reducing the risk of acquiring HIV infection. The level of protection did not differ by age, sex, regimen (TDF versus FTC + TDF) and mode of acquiring HIV (rectal, penile or vaginal) *(15)*. The level of protection was strongly correlated with adherence.

HIV infection

HIV infection was measured in 11 randomized controlled trials comparing PrEP to placebo, three randomized controlled trials comparing PrEP to no PrEP (such as delayed PrEP or "no pill") and three observational studies. A meta-analysis of data from 10 trials comparing PrEP with placebo demonstrated a 51% reduction in risk of HIV infection for PrEP versus placebo *(15,24,25)*.

Adherence

When all studies were analysed together, the results produced significant heterogeneity. The results from meta-regression conducted to evaluate whether certain variables moderated the effect of PrEP on reducing the risk of acquiring HIV infection demonstrated that adherence is a significant moderator.

When studies were stratified according to adherence levels (high, moderate and low based on proportion in the active arms with detectable drug in blood), heterogeneity in effectiveness was greatly reduced within adherence subgroups, demonstrating that most heterogeneity between studies can be explained by differing adherence levels. Within adherence subgroups, PrEP was most effective among the high-adherence group (defined as higher than 70% drug detection, but all studies in this group had adherence at or above 80%) and significantly reduced the risk of acquiring HIV in studies with moderate levels of adherence (41–70% drug detection). Among studies with low adherence (40% or lower drug detection), PrEP showed no effect in reducing HIV infection *(15)*.

Mode of acquisition

When studies were stratified by mode of acquisition (rectal, vaginal or penile exposure), PrEP showed similar effectiveness across groups. The relative risk of HIV infection for PrEP versus placebo for rectal exposure was 0.34 (95% CI 0.15–0.80). For penile or vaginal exposure, the relative risk of HIV infection for PrEP versus placebo was 0.54 (95% CI 0.32–0.90) *(15)*. Parenteral exposure to HIV was not analysed separately because only one study explicitly included people who inject drugs, and their exposure to HIV arose from sexual practices and incomplete access to sterile injection equipment.

Sex and gender

The 10 randomized PrEP trials reporting HIV outcomes included largely cisgender men and women. Women were included in six studies and men in seven studies. PrEP was effective for both cisgender men and women.

Since the recommendation was made in 2016, additional subgroup analyses of transgender women found PrEP to be effective when taken but there are still challenges with adherence *(26)*. A recent review found high willingness to use oral PrEP among transgender women *(27)*.

Safety

Ten randomized controlled trials comparing PrEP with placebo included data on any adverse event. Across studies, the rates of any adverse event did not differ for PrEP versus placebo. Similarly, there were no differences across subgroups, including mode of acquisition, adherence, sex, drug regimen, drug dosing or age.

Eleven randomized controlled trials comparing PrEP with placebo presented the results for any grade 3 or 4 adverse event. Across studies, there was no statistical difference in rates of any grade 3 or 4 adverse event for PrEP versus placebo and no statistical differences across subgroups, including adherence, sex, drug regimen, drug dosing or age *(15)*.

Several studies noted subclinical declines in renal functioning and bone mineral density among PrEP users *(28–30)*. These subclinical changes did not result in clinical events, were not progressive over time and reversed after discontinuing PrEP.

People who start PrEP may experience side-effects in the first few weeks of use. In 2019, a systematic review of 12 randomized controlled trials comparing PrEP with placebo found that people taking PrEP were more likely to report gastrointestinal adverse events, such as vomiting, nausea and abdominal pain *(23)*, although less than 10% of PrEP users across studies reported such adverse events. These side-effects are typically mild and self-limited.

Drug resistance

The risk of drug resistance to FTC was low overall – 11 people with FTC- or TDF-resistant HIV infection among 9222 PrEP users, or 0.1% – and this occurred mainly among people who were acutely infected with HIV when initiating PrEP: seven of the 11 people with FTC- or TDF-resistant HIV infection among 9222 PrEP users. The proportion of people with drug-resistant HIV did not differ in the PrEP and placebo groups among everyone at risk, although the number of events

was low (six people infected). Multiple HIV infections *(8–50)* were averted for every case of FTC resistance associated with starting PrEP in the presence of acute HIV infection *(15)*. Modelling the HIV drug resistance resulting from ART use is predicted to far exceed that resulting from PrEP use *(31)*. Although mathematical models inform the risk of resistance, their results rely on data from clinical trials and make assumptions about the risk of drug resistance selection during PrEP. A more recent review, conducted in 2019, similarly found that HIV drug resistance with PrEP is uncommon and breakthrough infection despite high adherence to PrEP is rare *(32)*. Countries are encouraged to monitor drug resistance against HIV drugs used for PrEP.

Sexual and reproductive health outcomes

At the time this recommendation was made, no evidence indicated that PrEP use led to risk compensation in sexual practices, such as decreased condom use or more sexual partners *(33,34)*. Since then, changes in sexual behaviour after PrEP initiation have not been widely observed, although this has been documented in some settings *(35–37)*.

PrEP does not appear to affect the effectiveness of hormonal contraception, although two studies found trends towards higher rates of pregnancy among oral contraceptive users who also took PrEP. When multivariate analysis accounted for confounders, this relationship was not significant. Oral PrEP was not associated with increased adverse pregnancy-related events among women taking PrEP during early pregnancy *(38,39)*. Drug–drug interactions between PrEP and gender-affirming hormone therapy for transgender women have been observed in some studies, with lower blood plasma TDF exposures among transgender women compared to cisgender men *(40–42)*. However, among transgender women and transgender men enrolled in directly observed daily dosing of PrEP, PrEP concentrations similar to cisgender men were observed *(43)*. Protective concentrations can be reached with daily use of oral PrEP even in the presence of gender-affirming hormones, and daily oral PrEP should be offered to transgender and non-binary people at substantial risk of HIV. Serum hormone concentrations are not affected by TDF + FTC PrEP use *(43)*.

Cost and cost–effectiveness

The HIV incidence threshold for cost-saving implementation of PrEP will vary depending on the relative costs of PrEP versus treatment for HIV infection and the anticipated effectiveness of PrEP. In some situations, PrEP may be cost saving, but other interventions may be more cost saving and scalable. Monetary costs should not be the only consideration, since staying free of HIV and having control over HIV risk has intangible value to people and communities. The cost–effectiveness of PrEP may decrease with declining HIV incidence in the context of universal treatment for HIV, but primary prevention, including PrEP, is essential to eradicate HIV, regardless of cost–effectiveness.

Offering PrEP in situations where the incidence of HIV is greater than 3 per 100 person-years is expected to be cost saving in many situations. Offering PrEP at lower incidence thresholds may still be cost-effective.

A review of cost–effectiveness studies for PrEP found that, in generalized epidemics, giving priority for PrEP use to people at substantial risk of acquiring HIV infection increases impact *(34)*. Some of these studies found PrEP to be cost-effective within the context of ART expansion; others found no benefit. In concentrated epidemics (such as among men who have sex with men in the United States of America), PrEP could have significant impact. Studies have found PrEP to be cost-effective depending on the cost of the drug and delivery systems when PrEP uptake is higher among people at substantial risk. Higher PrEP uptake and adherence have been observed among men who have sex with men in demonstration projects *(44,45)*. The results vary widely depending on epidemic type, location and model parameters, including efficacy, cost, HIV incidence and target population *(46)*.

Equity and acceptability

Preventing HIV among PrEP users will contribute to equitable health outcomes by sustaining their health and the health of their sexual partners. People at substantial risk of HIV are often underserved, have barriers to accessing health services and have few effective HIV prevention options. Access to PrEP provides opportunities to engage these individuals in health care, including sexual and reproductive health services. Broadening PrEP recommendations beyond narrowly defined groups (such as men who have sex with men and serodiscordant couples) enables more equitable access and is likely to be less stigmatizing than targeting specific risk groups. Effective PrEP services will reduce future treatment costs overall by preventing HIV infection in populations with high incidence.

PrEP acceptability has been reported in multiple populations, including cisgender women (and pregnant and breastfeeding women), serodiscordant couples, female sex workers, young women, people who inject drugs, transgender people and men who have sex with men. A qualitative literature review of 131 peer-reviewed articles and 46 abstracts *(47)* showed that individuals have considerable interest in accessing PrEP as an additional choice for HIV prevention. Population support for providing PrEP was based on knowledge of safety and effectiveness and the compatibility of PrEP with other prevention strategies.

Feasibility

Providing oral PrEP to diverse populations has proven feasible in multiple trial settings, demonstration projects and national programmes. Although placebo-controlled trials among cisgender women *(39,48)* found significant barriers to uptake and adherence, PrEP adherence among women has generally been high when open-label PrEP is provided *(49,50)*. The iPrEx OLE project and the Partners Demonstration Project both show that PrEP implementation is feasible for various populations, including men and women *(44,51)*. The PROUD study in the United Kingdom demonstrated that PrEP is feasible and effective and is not associated with significant changes in behavioural risk *(52)*. Other PrEP demonstration projects in Botswana, South Africa, Thailand and the United States of America confirm that protective levels of adherence are feasible for most PrEP users *(49,50,53–56)* although challenges remain to achieve high levels of adherence among some young people *(56)*. In 2019, following the publication of the initial recommendation, PrEP users were reported from 77 countries, and preliminary data suggests that considerable growth in global PrEP use continued in 2020 despite disruptions by the COVID-19 pandemic *(21)*. More than 100 countries in the world have adopted the WHO recommendations on PrEP into national guidelines *(21)*.

Implementation considerations

WHO published a comprehensive implementation tool for oral PrEP in 2017 *(16)*. This tool includes practical suggestions for clinicians, laboratory monitoring, pharmacy services, testing services, counselling, community engagement and integration of services (including ART, sexually transmitted infections, PEP and other sexual and reproductive health services). WHO will revise this implementation tool in 2021–2022.

As an additional HIV prevention option, PrEP should not displace other effective and well-established HIV prevention interventions, such as condom programming and harm reduction, but rather should be integrated into existing health services. Stigma is a driver of HIV and could decrease or increase depending on how PrEP is implemented. PrEP should be promoted as a positive choice among people for whom it is suitable and their communities, in conjunction with other appropriate prevention interventions and services, including sexual and reproductive health services. Legal environments in which the rights of people at substantial risk of HIV are violated may represent an important barrier to PrEP implementation.

Provider training

Health-care providers should be trained and supported to have conversations to explore sexual and injecting risk behaviour with their clients and help clients consider their risk of acquiring HIV and the range of prevention options, including PrEP. This involves providing respectful and inclusive services, a familiarity with techniques for discussing sensitive behaviour and a strong patient–provider relationship that enables discussions of facilitators and barriers to engagement in health-care services, adherence and self-care. Service providers should be aware of the emotional and physical trauma that people at substantial risk of acquiring HIV infection may have experienced *(57)*. The capacity for respectful work with people who have experienced trauma involves communication and skills development. Services that are appropriate for young people – especially young women and key populations – are essential for the success of all HIV treatment and prevention programmes, including PrEP. Service providers should consider all health, social, and emotional needs of people interested in and using PrEP and provide or refer to appropriate services as needed, including mental health support, intimate partner and gender-based violence services, family planning services, sexually transmitted infection testing and management, among others.

PrEP services can involve different types of health-care and lay providers for different aspects of PrEP service delivery. This includes nurses, pharmacists and lay and peer providers. Using a range of providers for PrEP service delivery has the potential to remove barriers to PrEP uptake and adherence, although adequate training of all service providers is necessary to ensure high-quality services.

Involving communities

Meeting the needs of populations at substantial risk of HIV infection requires the full participation of communities in developing and implementing programmes. The following are good participatory practices that apply to all priority and key populations.

- Recognize the leadership and resilience of priority and key populations in addressing the HIV epidemic at both the local and global levels and sustain their participation through adequate funding and support for community-based organizations.
- Ensure access to accurate knowledge and information about PrEP and early treatment by strengthening the capacity of the community-based organizations in educating and training their communities about their use.
- Promote and expand community-based services, especially services led by priority and key populations.
- Ensure that PrEP is offered as a choice, free of coercion and with access to other prevention strategies that may be preferred by the individuals at substantial risk.
- Increase political commitment to rights, including the rights of priority and key populations, by decriminalizing consensual sexual activity and gender expression.

Linking PrEP with other health and community services

People at substantial risk of acquiring HIV are often medically underserved, have few other effective HIV prevention options, and frequently face social and legal challenges. Providing PrEP may give opportunities for increased access to a range of other health services and social support, including reproductive and sexual health services (including managing sexually transmitted infections), and mental health services, primary health care and legal services.

Community-based organizations – especially those working with priority and key populations – should play a significant role in delivering PrEP by engaging people at substantial risk, providing information about PrEP availability and use and promoting links between PrEP providers and other health, social and community support services. Community-based

organizations can also be directly involved in delivering PrEP services, including by integrating peer and lay providers into services.

PrEP as part of combination prevention

PrEP should always be provided together with other HIV prevention options. Harm-reduction interventions – including access to sterile or new injection materials – are the mainstay of preventing HIV transmission through unsafe injecting practices, and such supplies should be made available to anyone using injected substances or medications. Condoms and lubricants should be made available, including for sex workers, who should be empowered to insist on their use *(58)*.

Recommendations for early initiation of ART and PrEP in these guidelines are expected to facilitate the identification of people recently infected with HIV. Whenever possible, people in their social and sexual networks should be offered HIV testing, treatment and prevention services. PrEP should be considered, in combination with other prevention services, for HIV-uninfected partners of recently diagnosed people.

HIV testing

HIV testing is required prior to starting or restarting PrEP and should be conducted regularly (such as every three months) during PrEP use. Additional HIV testing conducted after one month of PrEP use can detect acute infection that may have been present when PrEP was started. If the initial HIV serology test result is non-reactive (negative) and there is no history or signs or symptoms of an acute viral syndrome, the person could be offered and initiated on PrEP. If the person has had a recent high-risk HIV exposure (such as within the past 72 hours) they can be offered PEP and transition to PrEP after the completion of PEP and following additional HIV testing.

Frequent HIV testing during PrEP use is also an opportunity to provide sexually transmitted infection screening and management as well as other health services. Using quality-assured HIV testing, according to the national algorithm is important, and should include good counselling, linkage to earlier HIV diagnosis and treatment and minimize the risk of drug resistance during PrEP and PEP.

WHO recommends testing using the same strategy and algorithm for PrEP users as for other individuals. More expensive and complex testing strategies may hinder access and are unlikely to provide any greater benefit in settings where NAT assays or fourth generation serology assays are not routinely used for HIV diagnosis.

During COVID-19, some settings experiencing disruptions to HIV services began utilizing HIV self-testing to maintain essential services – including for initiating, and monitoring ongoing, PrEP. WHO has supported the use of HIV self-testing during COVID-19 as an interim measure and is currently reviewing evidence on the use of HIV self-testing for oral PrEP initiation and monitoring.

Monitoring renal function

Reduced kidney function, indicated by a creatinine clearance of <60 ml/min, is a contraindication for using oral PrEP containing TDF. A systematic review and individual patient data meta-analysis of global programme data *(59)* found that less than 1% of individuals who were screened before starting oral PrEP had abnormal creatinine clearance levels and less than 3% of oral PrEP users experienced a decline in creatinine clearance to <60 mL/min. Older individuals, especially those over 50 years, with baseline creatinine clearance of <90 mL/min and with kidney-related comorbidities such as diabetes or hypertension, had a higher probability of declining to abnormal levels of creatinine clearance. Less than 1% of oral PrEP users younger than 30 years experience abnormal creatinine clearance. Some programmes may opt to screen for creatinine clearance for all oral PrEP users. However, since creatinine elevation is so rare among individuals younger than 30 years with no kidney-related

comorbidities, creatinine screening may be considered optional in this group. To simplify the delivery and cost of PrEP, all individuals 30 years and older and those younger than 30 years who have comorbidities can be screened for serum creatinine once within 1–3 months after oral PrEP initiation. These suggestions by age and risk factors apply for both daily and event-driven dosing regimens.

More frequent screening than once is only suggested for individuals of any age with a history of comorbidities such as diabetes or hypertension, those 50 years or older and those who have had a previous creatinine clearance result of <90 mL/min. For these oral PrEP users, a further test after the baseline screening and every 6–12 months thereafter can be considered. When creatinine screening is conducted, any individuals with an estimated creatinine clearance of ≥60 mL/min can safely be prescribed TDF-containing oral PrEP. Waiting for creatinine screening results should not delay starting oral PrEP, since the results can be reviewed at a follow-up visit. Abnormal creatinine clearance of <60 mL/min should be repeated on a separate day before stopping TDF-containing oral PrEP. Other HIV prevention options should be discussed with the client. Creatinine clearance usually returns to normal levels after stopping PrEP, and PrEP can be restarted if creatinine clearance is confirmed to be to ≥60 mL/min 1–3 months after stopping PrEP. If creatinine clearance does not return to normal levels after stopping PrEP, other causes of renal insufficiency should be evaluated, such as diabetes and hypertension.

Hepatitis B and C

PrEP services provide a unique opportunity to screen for hepatitis B and hepatitis C infection and thus address multiple public health issues. Hepatitis B is endemic in some parts of the world where there is also a high burden of HIV. Testing oral PrEP users for hepatitis B surface antigen (HBsAg) once, at PrEP initiation, is preferred and has several advantages in these settings. Rapid point-of-care tests are available for HBsAg, and WHO has prequalified several rapid diagnostic tests. People with detectable HBsAg and clinical evidence of compensated or decompensated cirrhosis or people older than 30 years with persistently abnormal ALT levels and evidence of high-level hepatitis B replication (who do not have clinical evidence of cirrhosis) are eligible for long-term therapy for hepatitis B *(60)*. People at risk of acquiring hepatitis B with non-reactive HBsAg test may be considered for hepatitis B vaccination depending on endemicity and country recommendations *(61)*. The medications used for oral PrEP are active against hepatitis B. Withdrawing active therapy against hepatitis B can lead to virological and clinical relapse. Clinical relapse did not occur during or after PrEP use in trials that included people with chronic hepatitis B infection *(62,63)* and are considered very rare. hepatitis B infection is not a contraindication for daily oral PrEP use, but event-driven use of oral PrEP is inappropriate for individuals with chronic hepatitis B infection. Daily oral PrEP can be initiated before hepatitis B testing results are available.

Hepatitis C antibody testing can be considered at PrEP initiation and every 12 months thereafter depending on local epidemiological context, especially when PrEP services are provided to men who have sex with men, people who use drugs and people in prisons and other closed settings. Individuals with reactive serology test results should be referred for further assessment and treatment for hepatitis C infection *(64)*. Hepatitis C infection is not a contraindication for daily or event-driven oral PrEP use, and PrEP can be initiated before hepatitis C test results are available.

Adherence

Support for adherence should include information that PrEP is highly effective when used as prescribed. For daily oral PrEP users, brief client-centred counselling that links daily medication use with a daily habit (such as waking up, going to sleep or a regular meal) may be helpful. Tailored interventions to facilitate adherence among particular groups – such as young people – may be needed. Support groups for PrEP users, including social media groups, may be helpful for peer-to-peer sharing of experience and challenges.

People who start PrEP may report side-effects in the first few weeks of use. These side-effects include nausea, abdominal cramping or headache, are typically mild and self-limited and do not require discontinuing PrEP. People starting PrEP who are advised of this start-up syndrome may be more adherent.

PrEP should be used effectively – during periods of substantial HIV risk – but is unlikely to be for life. PrEP can be discontinued if a person taking PrEP is no longer at risk. It is not unusual for people to start and stop PrEP repeatedly depending on periods of higher and lower HIV risk. Engaging with PrEP users and community support groups is important to facilitate the recognition of circumstances that involve substantial risk of acquiring HIV. Such periods of risk may begin and end with changes in relationship status, alcohol and drug use, leaving school, leaving home, trauma, migration or other events *(55,65)*.

For cisgender men who have sex with men, event-driven PrEP is an effective strategy to reduce HIV risk. It entails a double dose of oral PrEP 2–24 hours before sex, followed by one dose each 24 and 48 hours after the first dose. This is sufficient to achieve high levels of protection against HIV. Event-driven PrEP is not an appropriate option for other PrEP users such as cisgender women, transgender women or transgender men having vaginal sex. Other populations are advised to take seven consecutive days of TDF-based oral PrEP to reach protective levels *(66)*. For event-driven PrEP users, a single dose of PrEP can be taken daily as long as potential sexual exposure to HIV continues, with a daily dose for each of the two days after the last sex act. For people using daily PrEP, it has been suggested that PrEP may be discontinued 28 days after the last potential exposure to HIV if people do not have continuing substantial risk for HIV. However, pharmacokinetic data suggest that PrEP may be discontinued earlier (i.e. seven days) after the last potential exposure. WHO will release revised guidance on this topic in 2021–2022.

People who report a potential high-risk exposure to HIV in the 72 hours before presenting for PrEP should be considered for PEP *(67)*. If substantial HIV risk continues after 28 days, PEP can be transitioned to PrEP.

Pregnancy and breastfeeding

Pregnancy and the postpartum period are characterized by substantial risk of acquiring HIV in some settings. HIV acquired during pregnancy or breastfeeding is associated with an increased risk of HIV transmission to the infant. An increasing body of evidence has demonstrated that TDF-containing oral PrEP is safe during pregnancy and breastfeeding *(68)*. Antenatal and postnatal care services offer an opportunity to integrate PrEP services for women at substantial risk of HIV, but more operational experience and research are needed to understand the unique needs and challenges of this population and how to best address them. Contraception services, safer conception management and links to antenatal care should be available when providing PrEP services for women and transgender men.

Research gaps

Since WHO recommended offering oral PrEP for people at substantial risk of HIV acquisition in 2015, there has been considerable global research on PrEP use, including pilot projects, demonstration studies, and national programmes for PrEP. In addition, oral PrEP was used in at least 77 countries in 2019 *(21)*. This expansion of oral PrEP services has generated substantial evidence on how to implement PrEP at scale but has also highlighted challenges with uptake, effective use and continuation of PrEP. Operational research is especially needed in diverse settings to generate demand for prevention services among adolescents and young people and support effective PrEP use. It is recognized that many PrEP users will not choose to take PrEP continuously for several years. Therefore, support to start, stop and restart PrEP related to periods of sexual risk is an important part of PrEP counselling. This includes innovative platforms such as using social media and mobile applications to engage with potential and existing PrEP users.

The global COVID-19 pandemic has accelerated a trend towards simplified, differentiated, and demedicalized oral PrEP service delivery. This includes using telehealth consultations for initiating and continuing PrEP and PrEP delivery at home and via pharmacies and other community-based locations. HIV self-tests have been used for initiating and continuing PrEP. In some places, peer and lay providers have been included in PrEP service delivery. All of these approaches have the potential to remove barriers to uptake and improve the effective use of PrEP. However, although the feasibility of these different forms of community-based PrEP delivery has been demonstrated in some settings, more operational research is needed on their effectiveness and scalability.

Some evidence indicates that using PrEP leads to changes in sexual practices that increase the risk for acquiring HIV. Although this form of risk compensation has been demonstrated in some settings, PrEP is likely to provide net benefits for HIV prevention, and potential changes in sexual behaviour underscore the need to integrate PrEP services with broader sexual and reproductive health services *(35)*. The broader impact of PrEP on sexual health, the use of other HIV prevention methods, emotional well-being and stigma against people living with HIV may vary according to social and cultural contexts and remains a topic of interest. Research on PrEP is encouraged to consider diverse biological, behavioural and social outcomes, and operational research is needed across settings on how to optimally integrate PrEP with other health and social services. Research has shown high prevalence and incidence of sexually transmitted infections among PrEP users, and integrating sexually transmitted infection screening and treatment into PrEP services could have broad sexual health benefits. Similarly, integrating PrEP and reproductive health services could lead to broad health improvements. Family planning services may offer an opportunity for providing PrEP services, but more evidence on real-world programme integration is needed. Moreover, while an increasing amount of evidence is highlighting that oral PrEP is safe during pregnancy and breastfeeding, more operational research is needed on how to provide PrEP services to pregnant and breastfeeding women.

PEP started after recent exposure can be transitioned to PrEP if substantial HIV risk continues, so PrEP and PEP services should be integrated where appropriate. Operational research on PrEP should also consider social outcomes such as gender-based and intimate partner violence and how to effectively provide gender-based and intimate partner violence services to people accessing PrEP services.

Globally, the largest numbers of PrEP users have been among cisgender men who have sex with men and cisgender women at risk of acquiring HIV. More research is needed on the specific needs of transgender women, transgender men and non-binary people, including additional support for adherence in this population and integration of gender-affirming care with HIV services, including PrEP. Research involving transgender men and non-binary people is particularly lacking, including how to improve awareness and uptake of and adherence to PrEP.

PrEP awareness and use among people who use drugs is limited, and more research on improving the engagement of people who use drugs with PrEP services is needed *(69)*. This includes more research on the feasibility and effectiveness of integrating harm-reduction and PrEP services. People in prisons and other closed settings and individuals recently released from those settings may also be at substantial risk of HIV infection in some geographical locations but are often not adequately reached by HIV prevention services, including PrEP.

WHO released guidance on event-driven PrEP for cisgender men who have sex with men in 2019, since evidence from randomized controlled trials showed high efficacy of non-daily PrEP dosing regimens. Although high use of event-driven PrEP has been reported in some settings, awareness and use of event-driven PrEP is low globally, which is partly because of slow adoption of event-driven PrEP into national guidelines. Further work at the country level is required on how to raise awareness and provide options for various oral PrEP dosing regimens. Moreover, because of the pharmacokinetics of TDF-containing oral PrEP, event-driven PrEP is

not recommended for cisgender women and transgender men or non-binary people who have frontal or vaginal sex. Event-driven PrEP may be an appropriate option for all cisgender men (not just those who have sex with men), but little is known on oral PrEP dosing preferences among heterosexual cisgender men. Moreover, event-driven PrEP may be appropriate for transgender men and non-binary people assigned female at birth who exclusively have anal sex. However, there has been very limited research involving members from these diverse populations on preferences for different PrEP dosing regimens and the pharmacokinetics of TDF-containing oral PrEP, including in the context of gender-affirming care *(49,53,54)*.

Oral PrEP has been shown to be cost-effective when provided to individuals at substantial risk of HIV in a range of settings and populations. However, differentiated and integrated oral PrEP service delivery, including in settings such as pharmacies and through community-based dispensing, and considering varying patterns of use, may offer opportunities for cost savings and efficiency. More research on the cost and cost–effectiveness implications of these evolving models of PrEP services is required.

With the dapivirine vaginal ring (see below), WHO has recommended additional PrEP modalities, and may recommend additional PrEP modalities, such as long-acting injectable cabotegravir, in the future. Research is needed on how to integrate these new PrEP modalities and dosing regimens into existing oral PrEP services, including cost and cost–effectiveness implications and on user preferences in diverse settings.

3.2.2 PrEP using the dapivirine vaginal ring

Recommendations (2021)

The dapivirine vaginal ring may be offered as an additional prevention choice for women[a] at substantial risk of HIV infection as part of combination prevention approaches *(conditional recommendation, moderate-certainty evidence)*.

[a] For the recommendation on the dapivirine vaginal ring, the term women applies to cisgender women, meaning women assigned female at birth. There is no research at this time to support the dapivirine vaginal ring for other populations.

Source: *Guidelines: updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (12).*

Background

PrEP delivered through a vaginal ring containing dapivirine, a novel non-nucleoside reverse-transcriptase inhibitor (NNRTI), as the active PrEP agent could provide an acceptable option for women who are unable or do not want to take oral PrEP. The dapivirine vaginal ring is a woman-initiated option to reduce the risk of HIV infection. It is made of silicone and contains dapivirine, which is released from the ring into the vagina slowly over one month. The ring should be continuously worn in the vagina for one month and then should be replaced by a new ring *(70)*. The risk of HIV-1 infection is reduced 24 hours after ring insertion *(71)*.

Adolescent girls and women in parts of sub-Saharan Africa continue to experience high HIV incidence. Current prevention options present challenges and barriers to use. The results from the recent ECHO trial *(72)* highlighted the high HIV incidence among women attending family planning clinics in parts of South Africa and Eswatini and that much greater focus is needed on integrating HIV prevention strategies for women receiving sexual and reproductive health services. In addition, adolescent girls and young women reported a preference for obtaining PrEP at service locations they are already comfortable attending, especially family planning and sexually transmitted infection services *(73)*.

Initial outcomes from oral PrEP programmes for women are mixed *(74)*. Some programmes report low uptake and low continuation *(75–77)*. Some women report facing challenges to taking daily oral PrEP. These include the need to take a pill every day, opposition to their taking oral PrEP from partners and side-effects that may occur during the first month of use. These concerns suggest that additional options are needed for PrEP delivery, including long-acting PrEP products that are potentially more discrete, do not rely on daily adherence and have less systemic adverse events. Supporting this evidence are studies demonstrating that women's needs and preferences for sexual and reproductive health are heterogeneous *(78)*. Expanding PrEP options to include a long-acting, woman-controlled option, such as the dapivirine vaginal ring, could help to meet unmet HIV prevention needs for women *(78,79)*.

Rationale and supporting evidence

Summary of review findings

A systematic review and meta-analysis of dapivirine vaginal ring trials demonstrated that the ring is effective in reducing the risk of acquiring HIV infection. Two randomized controlled trials – the Ring Study (IPM-027) *(80)* and ASPIRE (MTN-020) *(81)* reported that the dapivirine vaginal ring was approximately 30% effective in reducing HIV infection in intention-to-treat analysis. A subgroup analysis by age did not show efficacy among women 18–24 years old, who had lower adherence *(82)*. The results from two open-label extension studies – DREAM and HOPE – found increased efficacy, increased adherence and increased retention relative to the randomized controlled trials *(83,84)*. The results from one of the open-label extension studies indicated a 62% reduction in HIV transmission, comparing study results to the simulated control *(83)*. Further studies are underway or planned to help understand whether this lack of effect among younger women results from non-adherence or other factors and to identify ways to support adherence for younger women who choose the dapivirine vaginal ring for HIV prevention *(85)*. Safety and acceptability are also being studied among women 15–19 years old, who were not included in the trials. The dapivirine ring acts locally, and systemic absorption is low *(80)*. The trials reported no notable difference in the treatment and placebo arms of adverse events related to pregnancy, fetal outcomes and/or infant outcomes. However, since the number of pregnancies was small, ongoing trials are assessing further safety data during pregnancy and breastfeeding *(86,87)*.

Reduction in HIV infection

The evidence for HIV infection measured as an outcome in five studies was of moderate certainty. A meta-analysis of HIV infection reported in the two Phase III placebo-controlled randomized controlled trials (ASPIRE and the Ring Study) found a 29% reduction in HIV risk (95% CI 11–43%). This was similar to a pooled analysis using time-to-event data conducted by investigators from both trials that found a 27% relative reduction in HIV risk comparing the dapivirine vaginal ring to the placebo arms (95% CI 9–42%) *(88)*. Individually, ASPIRE found a 27% relative reduction in HIV risk (95% CI 1–46%) *(81)*, and the Ring Study found a 33% relative reduction in HIV risk (95% CI 5–53%) *(89)* for active dapivirine vaginal ring versus placebo arms.

For ASPIRE, efficacy increased when observations from the two research sites with low adherence were dropped, yielding a 37% relative reduction in HIV risk (95% CI 12–56%) *(81)*. ASPIRE conducted an age-stratified analysis excluding the two sites with low adherence and found that the dapivirine vaginal ring did not significantly reduce the risk of acquiring HIV among women younger than 25 years (the reduction in HIV incidence was 10%, 95% CI –41% to +43%), whereas HIV incidence was 61% lower for the dapivirine vaginal ring versus placebo among women 25 years and older (95% CI 32–77%) *(81)*. A post hoc analysis showed no efficacy and lower adherence among women 18–21 years old. The Ring Study also conducted

an age-stratified analysis but found no significant difference in risk reduction for women 21 years and younger versus women older than 21 years *(90)*. However, when the results across the two trials were pooled using individual-level data in analysis conducted by investigators, the reduction in the risk of acquiring HIV-1 was significantly higher among participants older than 21 years; no risk reduction was observed for participants 21 years or younger *(88)*.

The results from the two open-label extension studies, DREAM and HOPE, found increased efficacy, increased adherence and increased retention relative to the randomized controlled trials *(83,84)*. The results from DREAM indicated a 62% reduction in HIV risk compared with the simulated control, and the results from HOPE demonstrated a 39% relative reduction in HIV risk (95% CI 14–69%) compared to the simulated control. Of note, the participants in HOPE were given the choice of using the dapivirine vaginal ring at every study visit, whereas the participants in DREAM had to be willing to use the dapivirine vaginal ring as part of the study's eligibility criteria. In HOPE, 92% of the participants accepted the dapivirine vaginal ring at enrolment and 73% accepted the dapivirine vaginal ring for the duration of the study *(84)*.

Adverse events

All randomized controlled trials and open-label extension studies presented data on any adverse events with overall moderate-certainty evidence at 24 months. Overall, rates of adverse events were similar across study arms, and the safety endpoints from the open-label extension studies were similar to those found in the randomized controlled trials. When the results from the three randomized controlled trials were combined in a meta-analysis, the rates of any adverse event for dapivirine vaginal ring versus placebo arms did not differ significantly (RR = 1.0, 95% CI 0.95–1.06). When meta-analysis was restricted to the two Phase III randomized controlled trials, the results also showed no difference for the dapivirine vaginal ring versus placebo arms (RR = 1.02, 95% CI 0.98–1.06). In addition, when restricted to assessing differences between grade 3 or 4 adverse events across studies, the results of the meta-analysis showed no difference between the dapivirine vaginal ring and placebo arms (RR = 1.18, 95% CI 0.68–2.05; low-certainty evidence) *(91)*.

ASPIRE reported on study-related social harm, defining this as "nonmedical adverse consequences of dapivirine vaginal ring use or of trial participation more generally" *(92).* The results from ASPIRE found 94 instances of social harm with 4680 person-years of follow-up. Almost all (n = 87, 93%) were partner-related and were reported by 85 women, of whom 61% had disclosed study participation to their primary partners. Common triggers of social harm included the partner's discovery of the ring during foreplay or sex, notifying the partner of a sexually transmitted infection or the partner suspecting that the ring was associated with ill health, "promiscuity" or "witchcraft". The consequences in the small group of women experiencing social harm included destruction of the ring, physical violence or ending the relationship. About 60% of the cases of social harm were categorized as having a minimal impact on the quality of life. Younger women (18–26 years old) were more than twice as likely to experience social harm as older women, and reporting social harm was associated with short-term decreased product adherence *(92)*.

Drug resistance

ASPIRE, the Ring Study, DREAM and HOPE analysed resistance to NNRTIs. The prevalence of NNRTI-resistant infections among seroconverters within these studies ranged from 10% to 28%. When combined in meta-analysis, the results from the two Phase 3 randomized controlled trials show no increased risk for NNRTI-resistant HIV infection for the dapivirine vaginal ring compared to placebo arms (RR = 1.13, 95% CI 0.64–2.01; low-certainty evidence) *(91)*.

Sexual and reproductive health outcomes

All five studies reported on pregnancy incidence among participants, with no differences in incidence noted across the dapivirine vaginal ring and placebo arms. One analysis from ASPIRE evaluated contraceptive efficacy and found no differences for the dapivirine vaginal ring versus placebo arms (moderate-certainty evidence) *(93)*. However, the study identified significant differences in pregnancy incidence by contraceptive method, with women using oral contraceptive pills having much higher pregnancy incidence than those using implants or injectables.

Two analyses, one from ASPIRE and one from a research site in the Ring Study, examined pregnancy-related outcomes and found no difference in adverse pregnancy-related outcomes for the dapivirine vaginal ring versus placebo arms (very-low-certainty evidence) *(94,95)*. However, being on a stable form of contraception was an eligibility requirement for all studies included in this review, since the safety of taking dapivirine while pregnant and/or breastfeeding is unknown. In addition, all studies provided pregnancy tests to women monthly (quarterly during the latter half of the open-label extension studies), and participants immediately discontinued the study product if they became pregnant.

Behavioural outcomes, including incidence of curable sexually transmitted infections

One study described behavioural outcomes, including the number of sexual partners and condom use, observed at one research site in south-western Uganda within the Ring Study *(96)*. The study found no significant change in reports of non-condom use at last sex as reported at baseline and week 104 (64% and 67%, respectively; moderate-certainty evidence). Over the same time span, 57% reported two or more sexual partners at four weeks compared to 56% at 104 weeks (moderate-certainty evidence). Four studies, including the Phase II safety study, ASPIRE, the Ring Study and DREAM, reported on incidence rates of curable sexually transmitted infections identified post-baseline. No differences between study arms were reported (moderate certainty of evidence). However, one research site from the Ring Study found, significant decreases in diagnoses of Trichomonas vaginalis and Neisseria gonorrhoea infection from baseline to 104 weeks of follow-up *(96)*.

Cost and cost–effectiveness

According to the International Partnership for Microbicides, the current cost to produce the ring alone is US$ 7 per ring. It is anticipated that, in low- and middle-income countries, the ring will be provided free of charge to women at public health facilities. Based on several modelling and cost–effectiveness studies, the dapivirine vaginal ring is expected to cost less than oral PrEP since, from a provider perspective, it requires fewer health system resources. In previous studies addressing the cost–effectiveness of oral PrEP, the costs of HIV testing, creatinine clearance and hepatitis B surface antigen tests were all considered in the estimated cost of delivering oral PrEP. For delivering the dapivirine vaginal ring, the only required test is for HIV. One study from South Africa found that the dapivirine vaginal ring would be a cost-saving intervention for KwaZulu-Natal if the intervention were given priority for female sex workers *(97,98)*. Another modelling study from South Africa found that the dapivirine vaginal ring could have a modest impact on the HIV epidemic and be a cost-effective intervention, even with low efficacy, if uniform coverage across all high-risk groups was achieved *(99)*. Two other studies used the Goals model to assess the impact of the dapivirine vaginal ring across countries with a high burden of HIV infection and found that, although the dapivirine vaginal ring has potential to significantly affect epidemics, the impact is highly variable and depends on many factors, such as reaching UNAIDS targets and potential intervention cost *(100,101)*.

Feasibility

Multiple studies of the dapivirine vaginal ring have been conducted in countries in southern and eastern Africa, thus proving its feasibility across certain settings where the ring is intended

to be implemented. In addition to the safety study, two Phase 3 randomized controlled trials and two open-label extension projects, additional safety studies were successfully conducted among adolescent young women and postmenopausal women in the United States of America and among healthy women in Europe *(102–104)*. The dapivirine vaginal ring is relatively easy to transport and store. It does not require refrigeration and can be stored at room temperature. Several countries in sub-Saharan Africa (Kenya, South Africa, Zambia and Zimbabwe) are already considering initial steps on how to implement the dapivirine vaginal ring.

Acceptability and values and preferences

A review that included 11 articles and abstracts specifically relevant for vaginal rings containing dapivirine for HIV prevention found that the use of vaginal rings was highly acceptable (71–98% in randomized controlled trials and 62–100% in observational studies), and the vast majority of participants across studies reported that the rings are easy to insert and remove *(105)*. Most women disclosed ring use to their male partners, although some women feared violence or anger from partners if ring use was discovered *(106)*. The rings were not felt by 70–92% of participants during sexual intercourse and not felt by 48–97% of male partners. Ring acceptability increased over time as women became more comfortable using the ring and as the ring became more common in their community *(105)*.

Women expressed preferences for devices that were easily accessible, long-acting and partner-approved that could prevent both HIV infection and pregnancy and that could also be used without the partner's awareness, with minimal impact on sex, and with few side-effects *(105)*. Similarly, a review specific to the dapivirine vaginal ring use identified 21 studies, all conducted in sub-Saharan Africa, and found high acceptability. The review also noted that partner influence can affect ring use and that perceived community awareness and acceptance of the ring is important *(106)*.

A comprehensive systematic review and meta-analysis assessing the global acceptability of vaginal rings (agnostic to active pharmaceutical ingredient) similarly found that rings were highly acceptable *(107)*. The overall acceptability (proportion of women reporting a favourable experience) across 46 studies and 19 080 women was 87% (95% CI 83–91%). This review also found that most women who used the dapivirine vaginal ring liked it, whereas women with no direct experience using a dapivirine vaginal ring stated that they did not think they would like such a product.

The vast majority of women found the dapivirine vaginal ring acceptable. Among the 280 participants who participated in a safety study conducted in sub-Saharan Africa, 95% reported that they would be willing to use the ring if proven effective *(80)*. The results from safety studies among postmenopausal women and adolescents in the United States of America also found the ring highly acceptable *(104,108)*. Qualitative results from ASPIRE found that women grew more accepting of the ring once they used it and developed a sense of ownership and empowerment related to ring use. Women also found the ring easy to use and integrate into their daily lives *(109)*. The most commonly reported concerns were related to hygiene, especially during menses; potential negative health outcomes such as infertility; concerns the ring would get lost or stuck in the body; and concerns over partners feeling the ring during sex or not liking the ring *(80,110–114)*.

Equity

The Guideline Development Group judged that the introduction of the dapivirine vaginal ring as an additional prevention option would probably increase equity. The dapivirine vaginal ring offers an additional, discrete, woman-controlled biomedical HIV prevention option. Expanding PrEP options through offering the dapivirine vaginal ring, in addition to oral PrEP, could help meet the diverse needs and preferences of women. Evidence from the field of contraception has demonstrated an association between increased contraceptive choice and increased

contraceptive use among women. This has shown that increasing biomedical HIV prevention options could have a similar effect (increased options may lead to increased use) *(115)*. In addition, access to the dapivirine ring for women could also provide additional opportunities for sexual and reproductive health services.

Rationale for decision

The Guideline Development Group formulated a conditional recommendation favouring the dapivirine vaginal ring. The Group assessed that the benefits probably outweighed the harm based on the overall moderate-certainty evidence presented in the systematic review and meta-analysis, the cost–effectiveness of the dapivirine vaginal ring, widespread acceptability and demonstrated feasibility and the potential to increase equity as an additional prevention choice, noting some variability in younger age groups and concerns about use among pregnant and breastfeeding women because of a lack of sufficient evidence.

Implementation considerations

Comprehensive services

Similar to oral PrEP, the dapivirine vaginal ring should be provided to women in combination with other prevention interventions and health services. This should include provision of condoms, a range of contraceptive methods, testing and treatment of sexually transmitted infections and providing or referring to services that prevent and protect against gender-based violence. Where feasible, providing voluntary partner services should also be considered *(116)*. HIV testing should be provided before initiating the use of the dapivirine vaginal ring and every three months while using it as part of the service provision package.

Choice

Although the studies reviewed for this question did not directly compare oral PrEP to using the dapivirine vaginal ring, current evidence suggests that oral daily PrEP, when taken as prescribed, has greater efficacy for HIV prevention than the dapivirine vaginal ring. Oral PrEP should be offered at sites where the dapivirine vaginal ring is provided to enable women to make a choice. Women should be provided with full information and counselling on the available prevention options and their relative efficacy and safety and counselled to help them to make an informed choice regarding the best option for them.

The dapivirine vaginal ring for adolescent girls and young women

The data from the trials were not able to demonstrate efficacy among women younger than 21 years, who had low adherence to ring use. More data are needed to understand dapivirine vaginal ring use among younger women. Experience from oral PrEP services for adolescent girls and young women has shown that younger women may need more support, especially during the early stages of taking oral PrEP, to support continuation. This may be similar for dapivirine vaginal ring use, and studies are ongoing and/or planned in this age group to understand implementation issues and adherence challenges and to ascertain effectiveness, if these can be overcome.

The dapivirine vaginal ring for women from key populations

Although there is no experience with providing the dapivirine vaginal ring to women from key populations, including sex workers and women who use drugs, the dapivirine vaginal ring is expected to protect sex workers and women who use drugs from HIV transmission via vaginal sex. However, before focused implementation is planned for these populations, understanding and considering the values and preferences of women from key populations will be key to ascertain whether they would consider the dapivirine vaginal ring an acceptable and helpful additional prevention choice and, if so, what would be the most acceptable way to deliver it.

Service delivery

Currently there is no experience with providing the dapivirine vaginal ring outside of research and open-label extension projects. Careful consideration, including engagement with women and providers, is needed when deciding where the dapivirine vaginal ring could be offered. These could include reproductive health services, sexually transmitted infection services, contraception services, gender-based violence services and services specific to adolescent girls and young women or youth-friendly services and other services that make oral PrEP available to women. Special considerations will be needed for acceptable and safe approaches for women from key populations. Implementing demonstration projects can be helpful in furthering the understanding of the service delivery models best suited to offer the dapivirine vaginal ring.

HIV testing

Similar to using oral PrEP, HIV testing is required before the dapivirine vaginal ring is offered and should be conducted regularly (such as every three months) while using the ring. Unlike oral PrEP, no creatinine monitoring or hepatitis B testing is required for the safe use of the dapivirine ring. People who test HIV-negative but report substantial risk or who request the ring can be linked to HIV prevention services where the potential for dapivirine vaginal ring use can be assessed. The frequent HIV testing while using the ring is also an opportunity to offer contraceptives, provide sexually transmitted infection screening and management as well as other health services. Using quality-assured HIV testing according to the national algorithm is important and should include counselling and linkage to confirmatory HIV testing and treatment for anyone who has an HIV reactive (positive) test while using the ring. WHO recommends testing using the same strategy and algorithm for dapivirine ring users as for other individuals. More expensive and complex testing strategies may hinder access and are unlikely to provide any greater benefit in settings where NAT assays or fourth-generation serology assays are not routinely used for HIV diagnosis.

Adherence support

Similar to oral daily PrEP, the dapivirine vaginal ring needs to be used continuously during periods of risk for effectiveness. Adherence support should therefore be a key part of service provision. Flexible and tailored support will be needed, especially as women start to use this new product. The opportunity for frequent check-ins with a health (or lay) provider may be needed to support use as women start to use the product. Additional adherence support should be considered for younger women. Partner and peer support should also be considered.

Demand creation

The dapivirine vaginal ring is a new product. In many communities where women experience higher HIV risk, it could be provided even if there is little or no awareness or experience with using other vaginal ring products, such as the contraceptive vaginal ring. If a community is considering implementing the dapivirine vaginal ring, it will be important to develop an awareness programme for both the community and providers that is rolled out before and during introduction of the product. This should include engagement with women's networks, women's key population networks and the opportunity to understand concerns and respond to questions about this new product. Messages for men and male partners should also be considered. Some women reported that being able to discuss ring use with partners was supportive and helpful in continuing ring use.

Training and support for providers

The dapivirine vaginal ring is a new product. In settings with a high burden of HIV infection considering implementing the dapivirine vaginal ring, provider experience in offering vaginal ring products is unlikely. National programmes should work to provide adequate training support, since this will be needed to develop and provide this service. Ongoing mentoring and supportive supervision, as programmes continue, should also be considered. Understanding provider issues and concerns and addressing these concerns will be key.

Research gaps

Safety in pregnancy and breastfeeding

Monthly use of the dapivirine vaginal ring has been shown to be safe and effective for HIV prevention among non-pregnant women of childbearing potential. However, data on how dapivirine affects pregnancy outcomes and infants are limited.

Data from animal toxicity studies that evaluated various concentrations of dapivirine vaginal gel, including concentrations substantially higher than the concentration available in the vaginal ring, did not identify any adverse effects on the maternal animals or the developing embryo or fetus *(94)*.

In the MTN-020/ASPIRE trial, 169 of the 2629 women enrolled became pregnant during the trial *(94)*. From this small data set, dapivirine use in the periconception period does not appear to be associated with adverse effects on pregnancy or infant outcomes. However, additional safety studies are needed of dapivirine vaginal ring use during pregnancy and breastfeeding. Two ongoing studies (MTN-042 (DELIVER) and MTN-043 (B-PROTECTED)) will provide further safety data by the end of 2021 *(86,87)*. If these conclude that there are no safety concerns, continuing post-market surveillance activities will be needed to monitor for adverse pregnancy and fetal outcomes through the ARV drug pregnancy registration system.

Effective use among women younger than 21 years

A subanalysis of women younger than 21 years did not demonstrate efficacy in this age group, and adherence to the product was also low. Further studies are currently underway (such as MTN-034 (REACH) *(117)*) to assess adherence and safety in this age group and to understand barriers to use and ways to support adherence and continuation.

Acceptability among women from key population groups

There has been no research to date on implementing the dapivirine vaginal ring with key population groups, including sex workers and women who use drugs. Conducting values and preferences surveys with members of both communities will be important to understand their views on this intervention. Based on the results of these surveys, and if the communities feel that the dapivirine vaginal ring could be an important additional HIV prevention option, involving the community in designing and developing programmes will be critical.

The dapivirine vaginal ring as part of combination prevention

Women will be counselled on the dapivirine vaginal ring along with other prevention options such as daily oral PrEP. Male and female condoms and partner services must also be available and offered alongside the dapivirine vaginal ring. Some women may switch from oral daily PrEP to using the dapivirine vaginal ring and potentially back to oral PrEP use. These possible patterns of using ARV drugs for prevention are currently not known or understood and require careful support and assessment.

Some women may decide to use both the dapivirine vaginal ring and oral daily PrEP at the same time. Although using oral PrEP and the dapivirine vaginal ring together is probably safe, no evidence indicates that using them together will result in any additive advantage. Whatever the choice, adherence is important to optimize protection from either one. Further, inconsistent use of either or both when used simultaneously would be ineffective for HIV prevention. Using the dapivirine vaginal ring in combination with other prevention interventions and intermittent use of the dapivirine vaginal ring needs to be studied further, which could also include moving from oral PrEP to the dapivirine vaginal ring and back again according to circumstances.

It is not known whether introducing the dapivirine vaginal ring, and by increasing choice, will support more women at substantial HIV risk overall to access ARV drug–based prevention or whether the dapivirine vaginal ring will replace existing oral PrEP use for some users. Monitoring this will be important.

Cost and cost–effectiveness

Oral daily PrEP and the dapivirine vaginal ring are costly prevention interventions. This is why WHO suggests that these prevention options should be given priority for women at substantial HIV risk, since their use could have the greatest benefit and be most cost-effective. Further cost–effectiveness analysis using real-world data in various settings and population groups would be useful to guide future implementation for maximum impact.

3.3 Post-exposure prophylaxis

Recommendations (2016)

Overall

An HIV PEP regimen with two ARV drugs is effective, but three drugs are preferred *(conditional recommendation, low-certainty evidence)*.[a]

Adults and adolescents

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV PEP *(strong recommendation, low-certainty evidence)*.[a]

DTG is recommended as the preferred third drug for HIV PEP *(strong recommendation, low-certainty evidence)*.

When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for PEP *(conditional recommendation, low-certainty evidence)*.

Children[b]

AZT + 3TC is recommended as the preferred backbone regimen for HIV PEP for children 10 years and younger. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens *(strong recommendation, low-certainty evidence)*.[a]

DTG is recommended as the preferred third drug for HIV PEP with approved DTG dosing *(strong recommendation, low-certainty evidence)*.

When available, ATV/r, DRV/r, LPV/r and RAL may be considered as alternative third drug options for PEP *(conditional recommendation, low-certainty evidence)*.

[a] Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (13)*.

[b] The choice of ARV drugs for children will depend on the availability of approved dosing and age-appropriate formulations for children.

Background

WHO guidelines for HIV PEP, formulated in 2014, aimed to provide a simplified approach to delivering PEP, given the suboptimal uptake and completion of PEP *(67,118,119)*. The guidelines aimed to align recommendations for HIV PEP with the ARV drugs available in low- and middle-income countries for treating and preventing HIV.

The 2016 WHO consolidated HIV guidelines provided additional recommendations on eligibility, timing, prescribing and adherence support and clinical considerations *(13)*. The WHO clinical guidelines on responding to children and adolescents who have been sexually abused describe further clinical considerations in providing appropriate care to children and adolescents who have been sexually abused *(120)*. In 2018, new evidence provided information about the tolerability and completion rates of the WHO-recommended HIV PEP regimens and data on newer ARV drugs, notably DTG. In response, WHO provide updated recommendations on ARV drugs for HIV PEP *(121)*.

Rationale and supporting evidence

A systematic review completed in 2018 assessed the tolerability of HIV PEP and completion of different ARV drug regimens recommended by the 2016 WHO consolidated HIV guidelines *(13,121)*. The systematic review identified 16 studies reporting the outcomes of HIV PEP regimens using TDF + 3TC (or FTC) backbones *(121)*. All studies involved adults, and no additional evidence was retrieved for PEP regimens for children or adolescents. Overall, the highest completion rates for HIV PEP were reported for TDF + 3TC (or FTC) in combination with DRV/r (93%, 95% CI 89–97%) or DTG (90%, 95% CI 84–96%). These regimens were also associated with the lowest rates of discontinuation or substitutions because of adverse events (1%, 95% CI 0–2% for DRV/r; 1%, 95% CI 1–4% for DTG).

For adults, the Guideline Development Group recommends that DTG may be used as the preferred third drug for HIV PEP. This recommendation considered the high rates of PEP completion and low rates of adverse events as well as the established high tolerability of DTG when used in ART *(121)*. This preference also considered cost, current and anticipated availability, low potential for drug–drug interactions and the desirability of aligning with recommendations for ART. Alternative third drug options include ATV/r, DRV/r, LPV/r and RAL, with the choice to be based on considerations of tolerability and completion rates as well as cost, availability and acceptability *(121)* (Table 3.1).

Updated information since 2019

DTG was approved in June 2020 for all children older than 4 weeks weighing more than 3kg and available with dispersible tablets that can be easily administered for all children weighting less than 20 kg. For children weighting more than 20 kg, 50 mg adult film-coated tablets can be use.

The WHO 2014 guidelines on HIV PEP noted that data on using EFV in HIV PEP were lacking and that there are concerns about giving a drug associated with early central nervous system and mental health adverse events to HIV-negative people who may have anxiety related to HIV exposure. Since then, data have been published suggesting that EFV is associated with high rates of discontinuing HIV PEP because of central nervous system events *(122)*. EFV should therefore only be used as a third drug option when no other options are available.

For children, no new evidence has been published since the review carried out for the 2014 guidelines However, the recommendation to

provide DTG as a preferred drug option for this population (from four weeks and 3 kg) is now included, extrapolating from data for adults with the goal of aligning the recommendations for adults and adolescents.

Considerations for adolescent girls and women of childbearing potential

As part of comprehensive PEP services, all women should be offered pregnancy testing at baseline and follow-up. Emergency contraception should be offered to girls and women as soon as possible and within five days of sexual exposure. For women not wanting to take emergency contraception, an alternative to DTG should be provided *(121)*.

Assessing eligibility

HIV PEP should be offered and initiated as early as possible for all individuals with exposure that has the potential for HIV transmission, preferably within 72 hours. For individuals who may not be able to access services within this time, providers should consider the range of essential interventions and referrals that should be offered to clients presenting after 72 hours.

Eligibility assessment should be based on the HIV status of the source whenever possible and may include consideration of background prevalence and local epidemiological patterns.

The following types of exposure may warrant HIV PEP.

- Body fluids: blood, blood-stained saliva, breast-milk, genital secretions; cerebrospinal, amniotic, peritoneal, synovial, pericardial or pleural fluids. Although these fluids carry a high risk of HIV infection, this list is not exhaustive. All cases should be assessed clinically, and the health care workers should decide whether the actual exposure constitutes a significant risk.
- Types of exposure: (1) mucous membrane from sexual exposure; splashes to the eye, nose, or oral cavity and (2) parenteral exposures.

Exposure that does not require HIV PEP includes:

- when the exposed individual is already HIV positive;
- when the source is established to be HIV negative; and
- exposure to bodily fluids that do not pose a significant risk: tears, non-blood-stained saliva, urine and sweat.

In cases that do not require PEP, the exposed person should be counselled about limiting future exposure risk. Although HIV testing is not required, it may be provided if desired by the exposed person.

Clinical considerations

For PrEP, there is concern about the potential risk of hepatic flares among people with chronic hepatitis B once TDF-, 3TC- or FTC-based PEP is stopped. Assessment of hepatitis B infection status should not be a precondition for offering TDF-, 3TC- or FTC-based PEP, but people with established chronic hepatitis B infection should be monitored for hepatic flare after discontinuing PEP. Among people with unknown hepatitis B status and where hepatitis B testing is readily available, people started on TDF-, 3TC- or FTC-based PEP should be tested for hepatitis B to detect active hepatitis B infection and the need for ongoing hepatitis B therapy after discontinuing PEP.

NVP should not be used for PEP for adults, adolescents and older children because of the risk of life-threatening serious adverse events associated with HIV-negative adults using this drug.

For infants, NVP has been widely and safely used for HIV-uninfected infants for preventing vertical transmission of HIV and should be used for preterm babies or infants younger than four weeks old when DTG cannot be used. However, because the NVP toxicity profile beyond infancy remains unclear, its use should be avoided for children older than two years.

EFV is widely available as a third agent since it is used as part of the preferred first-line ART regimen. EFV is well tolerated for treatment but has limited acceptability for use as PEP since there are concerns about giving a drug associated with early nervous system and mental health adverse events to HIV-negative people who may have anxiety related to HIV exposure.

Full guidance on managing other conditions associated with possible exposure to HIV is provided in the 2014 *Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach (67)*.

Implementation considerations

The uptake and completion rates for HIV PEP are suboptimal, and the recommendations for HIV PEP regimens should be considered together with existing WHO recommendations aimed at improving completion rates for HIV PEP, including adherence support and providing a full 28-day course of medication at the first clinic visit *(13,67)*.

Choice of HIV PEP regimen should consider the ARV drugs already being procured within national HIV programmes. Additional considerations include the availability of heat-stable formulations, daily dosing, availability and affordability (Table 3.1).

People may be subject to ongoing high risk of exposure to HIV, leading to multiple prescriptions for PEP. In such situations, health-care providers should discuss with their clients the potential benefits of transitioning to HIV PrEP *(16,22)*.

Table 3.1 Characteristics of third drug options for PEP

Choice criteria	ATV/r	DRV/r	DTG	LPV/r	RAL
Discontinuation rate in HIV PEP	9.3%	0.9%	1.4%	5.2%	2.7%
Dosing schedule	Once daily	Once daily	Once daily	Twice daily	Once or twice daily
Availability as a heat-stable formulation	No	No	Yes	Yes	Yes
Accessibility in countries (registration status)	Low	Low	Moderate	High	Low
Acceptability to health providers	High	High	High	High	High
Affordability	Moderate	Moderate	High	Moderate	Low
Age indication	**>3 months**	**>3 years**	**>4 weeks**	**>14 days**	**Birth**

Source: *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines: supplement to the 2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (121).*

3.4 Infant prophylaxis

Good practice statement (2016)

ART should be initiated urgently among all pregnant and breastfeeding women living with HIV, even if they are identified late in pregnancy or postpartum, because the most effective way to prevent HIV vertical transmission is to reduce maternal viral load.[a]

[a] Whenever possible, all efforts should be made to identify HIV-infected pregnant women early enough to avoid the need for enhanced prophylaxis.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (13).*

Recommendations (2016)

- **Infants born to mothers with HIV who are at high risk of acquiring HIV[a] should receive dual prophylaxis with daily AZT and NVP for the first six weeks of life, whether they are breastfed or formula fed** *(strong recommendation, moderate-certainty evidence)*.
- **Breastfed infants who are at high risk of acquiring HIV[a], including those first identified as exposed to HIV during the postpartum period, should continue infant prophylaxis for an additional six weeks (total of 12 weeks of infant prophylaxis) using either AZT and NVP or NVP alone** *(conditional recommendation, low-certainty evidence)*.
- **Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP. If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT)** *(strong recommendation, moderate-certainty evidence for breastfeeding infants; strong recommendation, low-certainty evidence for infants receiving only replacement feeding)*.

[a] High-risk infants are defined as those:

- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; or
- born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load is available; or
- born to women with incident HIV infection during pregnancy or breastfeeding; or
- born to women identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (13).*

Background

Despite decades of progress in decreasing rates of vertical (mother-to-child) transmission, children continue to acquire HIV. Even with expanded treatment coverage for women with HIV, perinatal transmission continues to occur among infants born to women with HIV diagnosed in pregnancy or at delivery. Infants are also at risk of acquiring HIV during breastfeeding from a woman living with HIV. Roughly half of all newly infected children acquire HIV during breastfeeding. Although countries continue to make progress, challenges remain in retaining women living with HIV in health-care services and on effective ART throughout pregnancy and the breastfeeding period as well as detecting women who acquire during pregnancy and breastfeeding and preventing this from happening. Addressing these gaps requires continuing to emphasize promoting universal testing and treatment in the antenatal period and retesting HIV-negative women during pregnancy, at delivery and during breastfeeding to identify incident HIV, especially in settings with a high burden of HIV infection. In addition, it is important to consider the need for enhanced infant prophylaxis for the infants born to mothers that have not received early, effective ART.

The 2016 WHO consolidated HIV guidelines recommend a dual regimen of AZT and NVP for infants deemed to be at high risk of vertical transmission, which can be extended for up to 12 weeks for breastfeeding infants *(13)*. A high-risk infant is defined as an infant whose mother was first identified as HIV-infected at delivery or in the postpartum, infected during pregnancy or breastfeeding, started ART late in pregnancy or did not achieve viral suppression by the time of delivery (Fig. 3.1). All high-risk infants should receive dual drug prophylaxis (AZT plus NVP) for the first six weeks. For breastfeeding infants, this should be followed by either an extra six weeks of AZT plus NVP or an extra six weeks of NVP alone.

WHO guidelines on infant feeding *(123)* in relation to HIV reaffirm the position of WHO that the best way to prevent vertical transmission in the postpartum period and optimize infant survival is to ensure that mothers living with HIV are receiving ART, have suppressed viral loads and are able to breastfeed their infants for up to two years, with the infant being exclusively breastfed in the initial six months. If a mother receiving ART has suppressed viral loads, the risk of breast-milk transmission is very low and infant prophylaxis confers minimal additional benefit beyond 4–6 weeks of life.

Since the release of the 2016 WHO consolidated HIV guidelines, countries have adopted enhanced postnatal prophylaxis using a variety of different approaches to adapt to the country context and challenges. In about one third of AIDS Free priority countries (Burundi, Eswatini, Ethiopia, Ghana, Kenya, Mozambique and Zambia), enhanced postnatal prophylaxis has been adopted for all breastfeeding HIV-exposed infants, and the remaining countries have adopted enhanced postnatal prophylaxis for high-risk infants identified primarily based on maternal ART duration and, when available, maternal viral load close to delivery. Most countries opted for at least 12 weeks of prophylaxis, usually AZT + NVP for the first six weeks followed by NVP alone. Five countries (Eswatini, Kenya, Namibia, South Africa and Zambia) link the duration of enhanced postnatal prophylaxis to the maternal viral load and extend enhanced postnatal prophylaxis over the entire breastfeeding period when viral suppression is not achieved. Finally, in three countries (Botswana, United Republic of Tanzania and Zambia), administration of three drugs in a fixed-dose dispersible tablet formulation based on AZT + 3TC + NVP has been adopted to address the challenges of procuring individual liquid formulations.

Evidence for the recommendation

This recommendation is based on evidence from randomized clinical trials *(124)* and considers the risk–benefit ratio of enhanced postnatal prophylaxis: potential for increased drug toxicity versus additional protection from HIV transmission *(13)*. The systematic review *(124)* focused on studies that report on outcomes following the use of combined and/or

prolonged infant prophylaxis regimens compared with the current standard of care. Although some of the studies reviewed were conducted in settings in which formula feeding is the norm, the findings can still be applied to breastfeeding populations since intrapartum HIV transmission is an important driver of vertical HIV transmission in both settings. Four studies met the criteria for inclusion, of which two were randomized trials *(125,126)* and two were observational studies *(127,128)*.

- The intrapartum transmission rate was found to be significantly lower with the two-drug and the three-drug regimens versus AZT alone (126). Serious adverse events possibly or probably related to study drugs were more frequent with the three-drug regimen than with AZT-alone or the two-drug group.
- In a breastfed population, infants who received six months of NVP experienced a 54% lower transmission rate at six months compared with those who received only six weeks of NVP *(126)*. However, among the infants born to mothers receiving ART at the time of randomization, the postnatal transmission rate was extremely low and did not differ between those who received longer duration NVP prophylaxis versus placebo.
- In a large European cohort of "high-risk" mother–infant pairs, no difference was reported in serious adverse events between infants who received one, two or three drugs. When neutropaenia was compared between the two-drug and three-drug arms, there was a trend towards more events in the three-drug arm, but this was not statistically significant *(127)*.
- A single-arm study in non-breastfeeding infants of mothers who received less than eight weeks of antepartum ART in Thailand gave infant prophylaxis with AZT + 3TC + NVP for two weeks, followed by AZT + 3TC for an additional two weeks; no intrapartum infections were observed and the rate of serious adverse events among infants receiving intensified prophylaxis was lower than in a historical observational cohort (128).
- None of the studies reviewed addressed infants identified in the postpartum period or infants exposed to an incident HIV infection either during pregnancy or while breastfeeding. However, the findings of the systematic review could probably be applied to these settings as well.

The recommendations for extended prophylaxis for breastfeeding infants are predicated on maternal ART being initiated at or before the time when infant prophylaxis is begun (whether at birth or when maternal HIV is first detected postpartum), since infant prophylaxis is intended only to provide a bridge of protection to the infant during the period that maternal viral load is decreasing on ART.

Defining high-risk infants

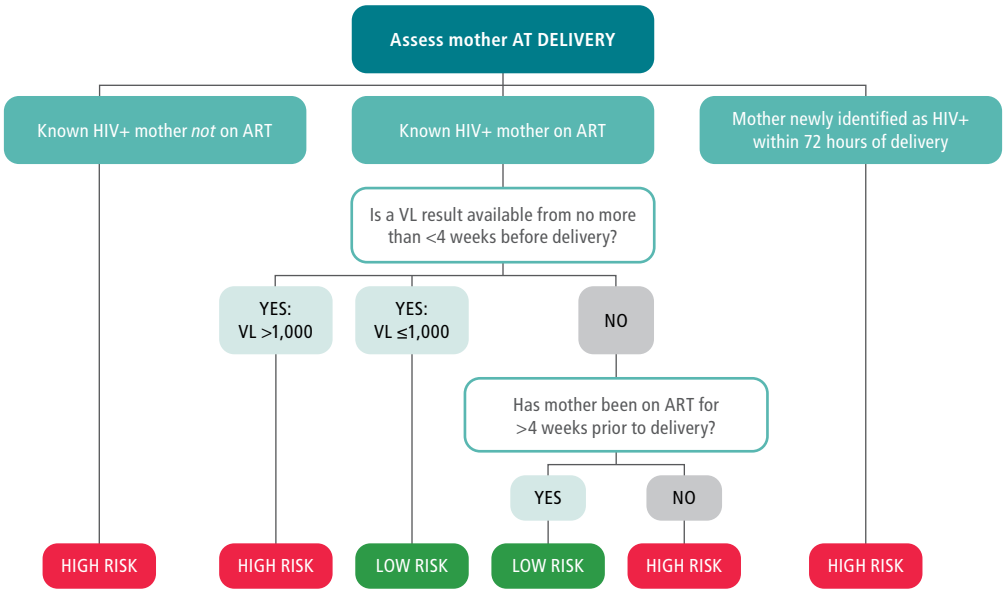
The 2016 WHO consolidated HIV guidelines acknowledge a range of factors to be considered when assessing risk, including examples from countries that stratify HIV-exposed infants according to risk *(13)*. Factors such as prolonged rupture of membranes, preterm delivery and low birth weight are no longer associated with increased risk of transmission when mothers are receiving ART. The critical determinants of transmission risk in the ART era are maternal viral load and duration of maternal ART.

Whenever possible, use same-day point-of-care testing for viral load testing of pregnant and breastfeeding women to expedite the return of results and clinical decision-making (see subsection 4.72). If this is not available, viral load specimens and results for pregnant and breastfeeding women should be given priority across the laboratory referral process (including specimen collection, testing and return of results). The 2021 WHO clinical guidelines *(12)* also state that for all pregnant women, regardless of ART initiation timing, viral load testing should be performed at 34–36 weeks of gestation (or at the latest at delivery) to identify women who may be at risk of treatment failure and/or may deliver infants at higher risk of perinatal transmission.

In this context, the following scenarios may be considered as working definitions of high risk:

- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery; or
- born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load is available; or
- born to women with incident HIV infection during pregnancy or breastfeeding; or
- born to women identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

Fig. 3.1 Algorithm for risk assessment at the time of delivery to help identify infants at high and low risk of infection



Implementation considerations

Providing multiple drugs to newborns is challenging from an operational perspective, and although AZT and NVP are proposed based on the available data, one is administered once daily and the other twice daily. Provider training will be critical to the successful uptake of these recommendations, and innovative approaches to dosing (such as using twice-daily dosing of NVP) may help to simplify administration. When the recommended regimen is not available or feasible, use of alternative options such as RAL, 3TC, LPV/r solid formulations or triple-drug fixed-dose combinations containing AZT, NVP and 3TC may be considered (the dosing recommendations can be found in Annex 1).

Consistent with the recommendations on early infant diagnosis, no specific approach to the testing of high-risk newborns is recommended. However, birth infant diagnostic NAT testing may be considered. In addition, infants who are first identified as HIV exposed postpartum have a high cumulative risk of already having acquired HIV by the time prophylaxis is initiated, and an HIV NAT test should be performed around the time of initiating prophylaxis. This will help to minimize the risk that extended prophylaxis among infected infants will lead to the development of resistance and will help promote linkage to timely initiation of ART.

Some programmes have adopted enhanced prophylaxis for all HIV-exposed infants. Although this may simplify decision-making, it increases costs and exposes many infants who may not need enhanced prophylaxis to added toxicity. This type of approach ought to be reserved for selected situations in which a majority of mothers are at high risk of transmitting HIV. Data on the average duration of ART at delivery and, where available, the proportion of pregnant women with viral load >1000 copies/mL at the end of the third trimester might help policy-makers to determine whether the potential benefit outweighs the added costs and toxicity. Even then, it should only be an interim measure while strategies to increase the coverage of maternal testing, early treatment and improved adherence are being implemented.

However, there are several situations where suppression of viral loads throughout the breastfeeding period cannot be ensured in the mother, for example:

- if a mother refuses or is unable to start or continue ART and intends to breastfeed her infant;
- if the provider knows the mother is poorly adherent to ART while breastfeeding; and
- if maternal viral load is known to be elevated when the infant prophylaxis regimen is about to be stopped.

There is no formal recommendation for these types of situations and no evidence to guide the best course of action. It is reasonable, however, to assume that infant prophylaxis serves as a back-up solution for preventing postnatal transmission of HIV, and national programmes could consider the merits of giving clinical providers the option of continuing infant prophylaxis beyond the recommended 6- or 12-week period. If this option is provided in the national guidelines, there ought to be clearly defined scenarios in which continuing prophylaxis is warranted. National guidelines should also emphasize that the best way to prevent breast-milk transmission of HIV is by optimal maternal treatment for the entire duration of exposure. Continuing prophylaxis should therefore be seen as an interim measure while efforts are made to support and improve maternal treatment adherence. Deciding to continue prophylaxis should consider the factors that led to poor maternal adherence since they may affect adherence to infant prophylaxis. Once stopped, infant prophylaxis should not be restarted if there are fresh concerns about maternal adherence. No evidence supports such an approach; instead the focus should be on determining why the mother was unable to remain adherent. If the decision has been made to continue infant prophylaxis, mothers and infants should be evaluated at regular intervals to assess the need for ongoing infant prophylaxis.

Research gaps

Potential areas for research include clinical and pharmacological studies to inform the development of improved ARV drug formulations, including fixed-dose combinations in appropriate doses for newborns and infants. Research into the use of alternative drugs for prophylaxis that are better tolerated and that may have greater efficacy for infant prophylaxis such as integrase inhibitors could also be considered. Studies to evaluate the clinical relevance of postnatal viraemic episodes in breastfeeding mothers and the relative contribution of such episodes to infant HIV infection are needed, coupled with evaluation of whether enhanced prophylaxis adds additional benefit in a population with a well-implemented effective maternal ART programme but known difficulty with adherence and viraemia in the postpartum period.

Finally, implementation science research to evaluate the optimal definition of high risk in the context of universal maternal ART and the impact of various service delivery models and how they affect adherence to enhanced postnatal prophylaxis and retention would be of great value.

Box 3.2 Improving service delivery and implementing a postnatal package of care

There are several barriers to the uptake of effective infant HIV services, and no single intervention can address all the barriers facing women and their infants at different times and places. Socioeconomic and traditional factors that keep mother–infant pairs together are among the enabling circumstances that improve service uptake. Programmes could benefit from combining effective interventions into service packages to support service provision and focus on the community engagement that supports uptake.

Interventions that have been proven to improve the provision and uptake of infant HIV services and the retention of mother–infant pairs include:

- client-focused interventions that provide support to individual clients using reminder text messaging, conditional cash incentives and male partner involvement; and
- health system-focused interventions, including measures to enhance the programme (point-of-care testing technologies, provider training and support, enhanced counselling services and peer support), to strengthen the health system (initiatives to improve quality and integrating maternal, newborn and child health and HIV services) and to support community-based services and health-care workers.

Promoting integration to reduce fragmentation of care for mothers and infants and ensure that infants remain in the testing cascade until final diagnosis should be a priority. Strong antenatal and well-baby care systems provide opportunities to strengthen service delivery for HIV-exposed infants. Integration within a well-established maternal, neonatal and child services platform, which traditionally provides services closest to clients, facilitates mother–infant pair follow-up and reduces the cost and time-visit burden on clients (integrated information systems that link mother and infant information improve client tracking and facilitate the continuity of care provision). Examples include longitudinal follow-up registers and cohort analysis and linkage with information on community services. Programmes should, however, consider the increasing burden on the maternal, newborn and child platform within the context of existing human resources and the challenges of changing services with new packages.

Community engagement and community-based services play an important role in supporting HIV-exposed infant care. These clear and highly context-specific services play a boosting role in supporting facility-focused services and include community-based HIV testing. The engagement of networks of women living with HIV has been effective in several countries and has been used to improve community HIV literacy to create demand, form support groups at the facility and community levels, strengthen linkage to care by escorting newly diagnosed clients to treatment clinics, conducting defaulter tracking and providing active follow-up of mother–infant pairs. In several settings, these interventions led to reduced loss to follow-up among mother–infant pairs.

Ensuring provision of a comprehensive integrated postnatal package of HIV services will promote delivery of a set of interventions that contributes not only to improved HIV outcomes but better early childhood development overall.

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ANTIRETOVIRAL THERAPY

04

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4. ANTIRETOVIRAL THERAPY

4.1 Introduction

In 2016, WHO strongly recommended initiating ART for all adults living with HIV regardless of WHO clinical stage and at any CD4 cell count. This "treat-all" recommendation has resulted in the scale-up of ART in more than 130 countries globally, accompanied by increased levels of availability of treatment monitoring. Treatment scale-up was further strengthened with the recommendation on rapid ART initiation in 2017, which promotes the initiation of ART within seven days of HIV diagnosis and the offer of same-day ART start. People with advanced HIV disease should be given priority for clinical assessment and treatment initiation *(1,2)*. This chapter summarizes the recommendations and supporting evidence. It also includes other key recommendations and information on the timing of ART, other coinfections, first-, second- and third-line regimens, known types of ARV drug toxicity and updates to the risk of neural tube defects in the periconceptional use of DTG. Chapter 5 covers the management of advanced HIV disease.

This chapter also includes key recommendations and clinical considerations for important subpopulations, including for people living with HIV who are pregnant or breastfeeding, adolescents, children and people with TB and other comorbidities.

4.2 Preparing people living with HIV for ART

Before people start ART, health-care providers should initiate a detailed discussion about their willingness and readiness to initiate ART, the choice of ARV drug regimen, dosage, scheduling, likely benefits, possible adverse effects and required follow-up and monitoring visits. For children living with HIV, this conversation should directly involve the caregiver and include discussion about disclosing their HIV status. Retesting all people living with HIV before initiating ART is recommended to ensure correct diagnosis of HIV infection. Any comorbidities and other medications being taken should always be considered before initiating ART to assess for possible interactions, contraindications or dose adjustment. A CD4 cell count should be taken when ART starts to determine whether the person has advanced HIV disease, but ART should not be delayed by waiting for the CD4 test result.

The choice to accept or decline ART ultimately lies with the person or their caregiver. Readiness to initiate ART should be reassessed at regular intervals; community and peer support can help a person to prepare and decide to start ART. If the person faces mental health or substance use issues or other potential barriers to ART initiation or adherence, appropriate support should be provided.

People starting treatment and their caregivers should be informed that the first ART regimen offers the best opportunity for effective suppression of viral loads, immune recovery and consequently clinical benefit and that successful ART requires taking all medications as prescribed. Delays in starting ART can have negative consequences, especially for people with TB or advanced immunosuppression who are at high risk of death. People should be advised that many adverse effects are temporary and treatable and that substitutions can often be made for the ARV drugs associated with adverse effects. In preparation for initiating treatment, psychosocial needs should be assessed. People receiving ART and their caregivers

should also be asked regularly about any other medications being taken, including herbal remedies and nutritional supplements.

People initiating ART should be given advice on safer sex, including using condoms and avoiding other high-risk activities such as sharing injecting equipment, to prevent transmitting HIV to other people.

4.3 What to expect in the first months of ART

Although ART is a lifelong commitment, the first months are especially important. Clinical and immune improvement and suppression of viral loads are expected when individuals adhere to ART, but opportunistic infections and/or immune reconstitution inflammatory syndrome may develop as well as early adverse drug reactions such as drug hypersensitivity. ART significantly decreases mortality overall, but mortality is also highest in the first three months of ART among people with advanced HIV disease and severe immunodeficiency (very low CD4 cell count) and existing coinfections and/or comorbidities, severely low haemoglobin, low body mass index or severe malnutrition. Poor adherence in this period is also associated with risk of early treatment failure and the development of drug resistance *(3)*.

Table 4.1 Recommended tests for HIV screening and monitoring and approaches to screening for coinfections and noncommunicable diseases

Phase of HIV management	Recommended	Desirable (if feasible)
HIV diagnosis and ART initiation	• HIV testing (serology for adults and children 18 months or older; infant diagnosis for HIV in children younger than 18 months) in accordance with WHO recommendations • CD4 cell count for identifying advanced HIV disease • Age-appropriate TB symptom screening • Cryptococcal antigen for adults and adolescents if CD4 cell count ≤200 cells/mm^3	• HBV (hepatitis B serum antigen) serology • HCV serology, screening for sexually transmitted infections for adults • Assessment for major noncommunicable chronic diseases and comorbidities (see Chapter 6) • Haemoglobin test if starting AZT • Serum creatinine and estimated glomerular filtration rate for starting TDF

4.4 When to start ART

Recommendations (2016)

ART should be initiated for all people living with HIV regardless of WHO clinical stage and at any CD4 cell count.

- **Adults** *(strong recommendation, moderate-certainty evidence)*
- **Pregnant and breastfeeding women** *(strong recommendation, moderate-certainty evidence)*
- **Adolescents** *(conditional recommendation, low-certainty evidence)*
- **Children living with HIV one year old to less than 10 years old** *(conditional recommendation, low-certainty evidence)*
- **Infants diagnosed in the first year of life** *(strong recommendation, moderate-certainty evidence).*

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3).*

Background and rationale

Global ART coverage for people living with HIV had reached 26 million people as of mid-2020 *(4)*. More than 120 low- and middle-income countries have adopted the "treat-all" policy *(5).* Although the median CD4 cell count at the time of ART initiation is increasing, about 25% of people living with HIV continue to present late to care, with low CD4 cell count and associated high early mortality rates, higher direct health-care costs and poor retention in care *(6,7).* Increasing knowledge of HIV status, strengthening links between testing and care, modifying health systems to manage patient volumes and ensuring optimal long-term retention and adherence remain significant challenges in many settings *(8).*

WHO HIV guidelines recommended initiating ART for all people living with HIV regardless of WHO clinical stage and at any CD4 cell count. The recommendation to start ART for all people living with HIV regardless of WHO clinical stage and at any CD4 cell count was based on a systematic review of three randomized trials (START, TEMPRANO and HPTN 052) and 17 observational studies *(3)*.

Costs, cost–effectiveness, equity, acceptability and feasibility

Initiating ART regardless of CD4 cell count was considered to be cost effective, equitable, acceptable and feasible *(3)*.

Considerations for subpopulations

People with advanced HIV disease

People with advanced HIV disease should be given priority for initiating ART since they are at high risk of death, particularly if resources are scarce. These people should be evaluated for the risk or presence of opportunistic infections such as TB and cryptococcal meningitis, but ART should be delayed only when meningitis or another central nervous system infection is suspected (see Chapter 5).

Pregnant and breastfeeding women

Providing ART to all pregnant and breastfeeding women living with HIV improves the woman's health outcomes, prevents the mother-to-child transmission of HIV and prevents the transmission of HIV from the woman to a sexual partner. Considering ART has individual health benefits for all adults, the recommendation applies to both breastfeeding and non-breastfeeding women.

Women who initiate lifelong ART, especially those with young children, may face considerable challenges in seeking regular HIV care and maintaining adherence to treatment. Efforts to scale up treatment require a holistic approach to women's lives and parallel investments in community-based support to improve women's treatment literacy, preparedness and agency to remain in follow-up and adhere to treatment.

Children

Infants and young children living with HIV have a high risk of poor outcomes, with up to 52% of children born with HIV dying before the age of two years in the absence of any intervention *(9)*. By five years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those observed among young adults *(10,11)*. Improved access to early infant diagnosis has increased the identification of infants living with HIV, but half the children who are eligible for ART are still not being treated, and ART coverage among children living with HIV lags behind that among adults: 53% versus 57% globally in 2020 *(6)*.

Since 2015, WHO has recommended initiating ART for all children with HIV. The recommendation to start ART immediately is conditional for children living with HIV from one to less than 10 years old because of limited evidence supporting ART initiation regardless of the clinical and immune conditions of children *(11–13)*. However, initiating ART provides significant programmatic advantages in practice, especially in settings with limited access to immunological testing, a high burden of HIV disease and low ART coverage among children *(14)*.

As ART is expanded to all children regardless of clinical and immune status, all children younger than five years are considered to have advanced HIV disease (Chapter 5) and should be given priority for treatment because of their higher risk of death and rapid disease progression.

Recently, more emphasis has been put on generating evidence on the early initiation of ART in newborns, with the goal of exploring the role of timing of ART initiation on improving outcomes and limiting the viral reservoir. For newborns, initiation within the first seven days of life results in a fourfold more rapid time to suppression of viral loads compared with initiating between eight and 28 days of life *(15)*. Similarly, younger age at ART initiation predicted more rapid suppression of viral loads in a cohort of infants from Europe and Thailand, with perinatal HIV acquisition and treatment initiation at a median of 2.9 months of age (16). Several studies have reported that early treatment of infants with perinatally acquired HIV is also associated with reduced size of viral reservoirs *(16–20)*.

These studies have provided further support for initiating ART as soon as the diagnosis is made, and when possible, during the first weeks of life, to limit reservoir formation. Treating full-term infants two weeks and younger and preterm infants is complex because of the limited data on the pharmacokinetics and appropriate dosing of ARV drugs in this age group; this area is being actively investigated *(21)*.

Research gaps

Adolescents and young women living with HIV face unique challenges in preventing the transmission of HIV to their children and attending to their own health needs, including poor access to reproductive health services, poor uptake of testing and poor retention in care. Operational research is urgently needed to identify the drivers of poor outcomes among adolescents to define how to provide adolescent-friendly maternal and newborn health services and to develop specific strategies to improve retention in care.

Although ART during pregnancy and breastfeeding provides clear public health benefits in terms of maternal health and preventing transmission to the child, the potential occurrence of adverse effects of ART (especially ART use during the preconception period) on pregnancy outcome and whether these adverse effects differ between ART regimens require further research. In addition, the potential long-term effects of fetal and infant exposure to maternal drugs are not fully understood. The overall risk of congenital birth defects appears to be similar to that of the general population for the currently recommended first-line ARV drugs; for newer drugs this remains an important topic for investigation.

Optimal service delivery models to ensure rapid identification and ART initiation among infants and children and strategies to provide an integrated package of care to reduce children's overall mortality are also needed. For example, the integration of ARV drug delivery in antenatal care and maternal, neonatal and childcare services (as opposed to referral to ART clinics) requires further implementation and assessment.

Significant knowledge gaps remain about the timing of ART initiation and the optimal ART regimen for newborns and how ART initiation in the neonatal period can be safely operationalized in the context of other competing priorities, lack of pharmacokinetic data for dosing of more optimal drug regimens and lack of appropriate training for frontline care providers.

4.5 Timing of ART

4.5.1 Rapid ART initiation

Recommendation (2017)

Rapid ART initiation[a,b] should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment *(strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).*

ART initiation should be offered on the same day to people who are ready to start *(strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).*

[a] Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

[b] See Table 4.2 for clinical considerations for individuals being evaluated for rapid ART initiation.

Source: *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017 (1).*

Good practice statement (2016)

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and should promote engaging and supporting people and families to play an active role in their own care by informed decision-making.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3).*

Background

WHO guidelines published in 2017 *(1)* recommend initiating ART within seven days after HIV diagnosis and that people with advanced HIV disease be given priority for assessment and ART initiation. The guidelines further recommend offering ART initiation on the same day to people who are ready to start *(1).* However, people presenting for the first time or those returning to care should undergo history and clinical examination to evaluate for opportunistic infections (such as signs and symptoms of TB meningitis and signs and symptoms suggesting cryptococcal meningitis) before rapid ART initiation is offered. Immediate ART initiation is contraindicated among people living with HIV who have cryptococcal meningitis because of the increased mortality presumed to be caused by immune reconstitution inflammatory syndrome in the central nervous system.

- Among people living with HIV with signs and symptoms suggesting TB, except for central nervous system disease (meningitis), initiate ART while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if TB is confirmed.
- For those with cryptococcal meningitis, ART initiation should be deferred until there is evidence of a sustained clinical response to antifungal therapy and after four weeks of induction and consolidation treatment with amphotericin B–containing regimens combined with flucytosine or fluconazole or after 4–6 weeks of treatment with a high-dose fluconazole induction and consolidation regimen *(conditional recommendation, low-certainty evidence).*
- For people with signs and symptoms of meningitis, ART should be delayed pending the results of lumbar puncture.
- No prospective evidence supports decisions about when to start ART among asymptomatic people with cryptococcal antigenaemia after initiation of pre-emptive antifungal therapy. Guidelines from the Southern African HIV Clinicians' Society *(22)* recommend starting ART two weeks after starting fluconazole, and consideration is being given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis among people who test positive for blood cryptococcal antigen.

Rationale and supporting evidence

Rapid ART initiation

A systematic review identified three randomized controlled trials *(23–25),* 11 observational studies *(26–36)* and five qualitative studies *(37–41)*. Across the randomized trials with rapid initiation, the likelihood of starting ART within 90 days of eligibility (RR 1.3, 95% CI 1.23–1.39) and within 12 months of eligibility (RR 1.09, 95% CI 1.05–1.13) was increased. Retention in care at 12 months (RR 1.12, 95% CI 0.99–1.28), suppression of viral loads at 12 months (RR 1.18, 95% CI 1.08–1.29) and mortality (RR 0.47, 95% CI 0.24–0.93) were influenced positively. In the observational studies, offering rapid ART initiation resulted in a greater likelihood of having started ART within three months (RR 1.53, 95% CI 1.11–2.10); however, no evidence indicated that offering rapid ART resulted in a greater likelihood of remaining in care (RR 0.97, 95% CI 0.79–1.18), and the risk of being lost to follow-up after ART initiation tended to be increased (pooled RR: 1.85, 95% CI 0.96–3.55).

ART initiation for individuals suspected of having HIV-associated TB

A systematic review identified four randomized clinical trials (three clinic-based and one community-based) reporting on TB screening approaches to determine whether a person may start same-day ART *(42–46)*. The main findings from these studies were that 7–47% of people living with HIV presenting for same-day ART had TB symptoms (WHO symptom screening) and that initiating ART among people living with HIV with TB symptoms was feasible.

Very little information is available on the potential harm of same-day ART initiation in the presence of TB symptoms; however, these studies support the feasibility of this approach. Among people living with HIV (unknown TB status), same-day start is acceptable and recommended by WHO *(47)*. Initiating ART while investigating for TB is expected to result in increased resource requirements in terms of personnel time and possible need for managing incident immune reconstitution inflammatory syndrome. Experience in implementing rapid ART initiation among people living with HIV with TB symptoms (except for TB meningitis) in countries such as Malawi also suggests that this approach is feasible *(48)*.

ART initiation may proceed while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if a diagnosis of TB is made. The approach to rapid ART initiation must include assessing advanced HIV disease and related clinical management. The Guideline Development Group stressed the importance of excluding people living with HIV with signs and symptoms of meningitis and screening for cryptococcal antigen among those with advanced HIV disease before initiating ART, since immune reconstitution inflammatory syndrome among these people is more common and potentially life-threatening.

Comparing benefits and harm

Linking people testing positive for HIV to ART services is programmatically challenging *(49,50)*. The offer of rapid initiation, including same-day ART, increases the number of people starting ART, reduces mortality and may further reduce both mother-to-child transmission and transmission to HIV-negative partners. However, possible harm identified includes the potential for missing clinical conditions requiring management before ART, the risk of immune reconstitution inflammatory syndrome among severely immunosuppressed people and the potential for people to feel coerced to start when they are not ready mentally. If health-care workers feel pressured to meet targets for ART initiation, this may lead to undue pressure on people to start ART as soon as possible. Special consideration should also be given to women in some settings if they may not be able to make the decision to start lifelong therapy independently.

Costs, cost–effectiveness, equity, acceptability and feasibility

At the time the recommendation was formulated, three studies, two from South Africa and one from China, provided costing evidence that rapid initiation is cost effective and sustainable *(36,51,52)*. Rapid initiation may improve the equity and accessibility of ART for people who may otherwise be lost to follow-up during ART preparation sessions *(24)*. Preparing children and their caregivers to initiate ART, especially when syrups are prescribed, may require additional support, but rapid ART was considered to be broadly acceptable for most populations. Health-care workers and programme managers reported rapid or same-day initiation as being feasible across all populations, despite some specific challenges in key populations.

Clinical considerations when implementing rapid ART initiation or same-day initiation

People presenting for the first time or those returning to care should undergo history and clinical examination to evaluate for opportunistic infections (such as signs and symptoms of TB and signs and symptoms suggesting meningitis) before rapid ART initiation is offered. Although no longer a requirement for ART initiation, baseline CD4 cell count testing should be performed to determine whether the person has advanced HIV disease.

Table 4.2 outlines specific considerations for rapid ART in subpopulations. People with advanced HIV disease (CD4 cell count <200 cells/mm^3) should receive the package of care for advanced HIV disease outlined in Chapter 5.

Considerations when implementing rapid ART among individuals suspected of having HIV-associated TB

Close follow-up is required to ensure that TB diagnostic results are acted on rapidly and that immune reconstitution inflammatory syndrome and other adverse events are recognized and managed across populations. HIV programmes must also ensure adequate training of health-care personnel to recognize TB signs and symptoms among vulnerable people such as infants and children, rule out central nervous system signs and symptoms and assess for and manage both advanced HIV disease and locally endemic coinfections *(53)*. Ensuring the availability of rapid diagnostic tests for TB and systems for timely return of results (ideally same-day return if feasible) is also important. Patient education and support for early recognition of immune reconstitution inflammatory syndrome, adverse events and adherence counselling are needed.

Considerations for children living with HIV who are hospitalized or severely ill

Two trials have assessed rapid initiation of ART for very sick children living with HIV. In the first study from South Africa, young children (median age 23 months) with severe acute malnutrition were randomized to receive ART within 14 days of admission or delay it until nutritional recovery. The results suggested that delayed ART improved immune recovery, suppression of viral loads and anthropometric measures, but the treatment arms did not differ in mortality *(54).* In the second trial in Kenya, hospitalized children living with HIV (median age 23 months) were randomized to start ART within 48 hours versus 7–14 days. Early mortality was extremely high among hospitalized children with HIV, and urgent ART (within 48 hours) did not improve survival. However, although the treatment arms did not differ in mortality, the authors concluded that rapid treatment (whether immediate or within 14 days) is safe, and prompt initiation of ART after medical stabilization of coexisting illness is essential to reduce the very high mortality observed overall, with 21% of children dying during six-month follow-up *(55,56)*. Overall, although ART initiation remains a priority, especially for children younger than five years and children who present with symptoms, timely provision of appropriate care for clinical conditions requiring acute management is the first priority.

Research gaps

Rapid ART initiation

Further implementation research is needed to assess the adaptations health-care systems require to provide rapid or same-day ART initiation in programmatic settings. This should include analysing how clinical readiness is assessed, including the package of diagnostics, prophylaxis and screening interventions for advanced HIV disease, and how psychosocial readiness is assessed in the context of busy operational settings as well as approaches to support treatment adherence. Important clinical questions related to situations in which ART is started before laboratory results (CD4 cell count, cryptococcal antigen testing) being obtained and the actions that are then required once the results are received require further investigation. Evidence on how rapid initiation affects long-term outcomes in programme settings is limited, and there is no evidence about the impact of rapid ART among adolescents and children living with HIV who require specific counselling interventions to address both disclosure of HIV status and to ensure correct administration and dosing of ART by caregivers. Approaches to supporting rapid initiation in key populations and those reinitiating ART warrant further research.

Other research gaps include how initiating ART among people with TB symptoms (excluding those with signs and symptoms of meningitis) affects mortality, TB and HIV outcomes, adverse events, immune reconstitution inflammatory syndrome, retention in care and ART adherence. Finally, it is important to examine the role of prophylactic corticosteroids to reduce the incidence of immune reconstitution inflammatory syndrome among people living with TB and HIV in public health settings and the timing of this prophylaxis.

Table 4.2 Summary table for the timing of ART initiation among people living with HIV

Population or clinical status	Timing of ART initiation
Adults, adolescents and children living with HIV with no signs and symptoms of TB	Rapid ART initiation on the same day should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment.
Adults, adolescents and children living with HIV with suspected TB	Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment and to people living with HIV with signs and symptoms suggesting TB. Except for central nervous system disease (meningitis), initiate ART while rapidly investigating for TB, with close follow-up within seven days to initiate TB treatment if TB is confirmed.
Adults, adolescents and children being treated for HIV-associated TB (including multidrug-resistant TB)	ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.
Adults, adolescents and children being treated for HIV-associated TB meningitis (either clinically or with a confirmed laboratory test)	ART should be delayed at least four weeks (and initiated within eight weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered adjuvant treatment for TB meningitis.
People living with HIV who are already diagnosed with TB but not receiving ART or treatment for TB	TB treatment should be initiated first, followed by ART as soon as possible within the first two weeks of treatment
People living with HIV with cryptococcal meningitis	Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment. Thus, ART should be initiated between 4–6 weeks after undergoing antifungal treatment.
People living with HIV with histoplasmosis infection	ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven.

Sources:

a. *Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (57).*

b. *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017 (1).*

c. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3).*

d. *Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children (58).*

e. *Guidelines for treatment of drug-susceptible tuberculosis and patient care – 2017 update (59).*

f. *Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV (53).*

g. *WHO consolidated guidelines on tuberculosis. Module 2: screening – systematic screening for tuberculosis disease (60).*

h. *WHO consolidated guidelines on drug-resistant tuberculosis treatment (61).*

4.5.2 Timing of ART for adults, adolescents and children being treated for HIV-associated TB

Recommendation (2021)

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a]

Adults and adolescents
(strong recommendation, low- to moderate-certainty evidence)

Children and infants
(strong recommendation, very-low-certainty evidence)

[a] Except when signs and symptoms of meningitis are present.

Source: *Guidelines: updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (62).*

Background

Since 2010, WHO has recommended that ART be started as soon as possible and within eight weeks of initiating TB treatment *(strong recommendation, high-certainty evidence)*. In 2013, WHO added a recommendation to initiate ART within two weeks among those with CD4 count less than or equal to 50 cells/mm3 (except for children for whom previous recommendations remained unchanged because of the lack of specific evidence) *(3).* In 2017, based on a systematic review of evidence that earlier ART initiation resulted in reduced morbidity and mortality *(1)* (not specifically for people living with HIV with TB), WHO recommended offering rapid ART initiation within one week, and the same day if ready, for most people diagnosed with HIV, including adults, adolescents and children *(1)*, with stated cautions for those with signs and symptoms of meningitis and a brief delay if TB is suspected.

Rationale and supporting evidence

Summary of review findings

Four studies *(63–65)* (personal communication, Corinne Merle, WHO, 2021) provided information on ART initiation within two weeks of starting TB treatment and between two and eight weeks. Nine studies informed a comparison of ART initiation within two weeks of TB treatment initiation versus initiation between two and eight weeks. An additional comparison of ART initiation before and after four weeks was included and was informed by nine studies.

Moderate-certainty evidence indicates that mortality may be similar with ART initiated within two weeks of TB treatment versus ART initiated between two and eight weeks (risk difference = –0.01; 95% CI –0.06 to 0.04), which can be interpreted as 1 less death per 100 people, ranging from 6 fewer deaths to 4 more deaths per 100 people.

In a subanalysis of people with a CD4 cell count less than or equal to 50 cells/mm^3, low-certainty evidence indicated that mortality may not differ (3 fewer deaths per 100 people, 95% CI from 10 fewer to 4 more per 100) with ART initiated within two weeks of TB treatment versus between two weeks and eight weeks. Among the subgroup with CD4 cell count

greater than 50 cells/mm^3, low-certainty evidence indicated that mortality may be similar with earlier ART initiation (2 fewer deaths per 100, 95% CI from 7 fewer to 4 more deaths per 100 people) with ART initiated within two weeks of TB treatment versus between two weeks and eight weeks.

Low-certainty evidence indicated that AIDS-defining events (for all CD4 cell counts) may be similar with ART initiation within two weeks of TB treatment initiation versus between two and eight weeks (2 fewer AIDS-defining events per 100 people, 95% CI 6 fewer to 3 more per 100 people).

Among people living with HIV with any CD4 cell count, low-certainty evidence indicated that viral load suppression may not differ between people initiating ART within two weeks versus between two and eight weeks (1 person with viral load suppression less per 100 people, 95% CI from 3 fewer to 6 more per 100 people).

Very-low-certainty evidence indicated that the incidence of immune reconstitution inflammatory syndrome events may be increased among people offered ART initiation within two weeks from TB treatment initiation versus between two and eight weeks (7 more events per 100 people, 95% CI 3 fewer events to 17 more events per 100 people). However, mortality related to immune reconstitution inflammatory syndrome was uncommon.

Despite theoretical concerns about increased risk of immune reconstitution inflammatory syndrome in DTG-based regimens, the INSPIRING trial *(66)* reported that the incidence of immune reconstitution inflammatory syndrome was similar between the DTG and EFV arms (in this small trial of safety and efficacy of rifampicin-based TB treatment and ART initiated within eight weeks). These findings were consistent with the 2019 network meta-analysis undertaken to inform the 2019 WHO ARV drug guidelines update, with the safety of DTG examined among people with both TB and HIV. No deaths were reported in either arm (DTG versus EFV), fewer severe adverse events in the DTG arm (odds ratio: 0.61, 95% CI 0.17–2.24), with low-certainty evidence *(67)*. The REALITY trial among people with advanced HIV disease included RAL as an additional option and also did not find any increased incidence of immune reconstitution inflammatory syndrome *(68).* Box 4.1 details specific considerations for cryptococcal and TB meningitis.

Box 4.1. Importance of screening for signs and symptoms of meningitis

Among people living with HIV with TB meningitis or other forms of meningeal infection such as cryptococcal meningitis, earlier ART is associated with more severe adverse events and increased mortality with cryptococcal meningitis. For people living with HIV and TB meningitis, immediate ART is associated with more severe adverse events compared with initiating ART two months after the start of TB treatment.[a]

- ART should be delayed by 4–6 weeks of ART following initiation of treatment for cryptococcal meningitis. Use of steroids is not recommended.[a]
- ART should be delayed at least four weeks (and initiated within eight weeks) after treatment for TB meningitis is initiated. Corticosteroids should be considered adjuvant treatment for TB meningitis.[b]

Sources: [a] *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (1).* [b] *Guidelines for treatment of drug-susceptible tuberculosis and patient care – 2017 update (59).*

Children and infants

The systematic review did not identify any study including children. The Guideline Development Group considered it appropriate to extrapolate the supporting evidence from the adult population and to extend the overall recommendation of earlier initiation to children, acknowledging the very low-certainty evidence resulting from considerable indirectness. The Guideline Development Group highlighted the urgency of initiating ART in this subgroup, especially young children *(69)*. Strong evidence indicates increased morbidity and mortality when ART initiation is delayed among infants and young children regardless of CD4 count *(13)*.

Pregnant and breastfeeding women

The review did not identify any studies that included pregnant and breastfeeding women. However, the Guideline Development Group noted that earlier ART was unlikely to increase harm in this population, and the well-known and demonstrable benefits of earlier ART for both the mother's health and the child's health, with reduced vertical transmission of HIV, outweighed potential harm.

Cost and cost–effectiveness

No important differences in resource use are expected for initiating ART earlier among people living with HIV starting TB treatment, since everyone is anticipated to start ART within a period of a few months. However, the increased incidence of immune reconstitution inflammatory syndrome associated with earlier ART initiation may require additional resources to accommodate an increased rate of hospital admissions. However, overall, this was not considered a major concern.

Feasibility

Several countries have already adopted a policy of earlier ART initiation for people with TB. For example, Malawi's HIV 2018 guidelines recommend initiating TB treatment and ART at the same time and those of Zambia (2020) and Uganda (2020) within two weeks of TB treatment for people living with HIV with TB regardless of CD4 cell count, including among children. This evolution of policies suggests that adopting and implementing the intervention is feasible.

Acceptability, values and preferences

The acceptability of earlier ART start among all people living with HIV was reviewed in preparation for the 2017 guidelines on advanced HIV disease and rapid ART initiation, and the intervention was generally perceived to be acceptable to people living with HIV and providers *(70)*.

WHO conducted a survey of values and preferences among a small sample of people living with HIV, health-care workers caring for people living with HIV and HIV programme managers. This survey indicated that earlier ART (including same-day initiation with TB treatment initiation) was acceptable to 70% of people living with HIV, but 42% were very worried about side-effects if both treatments started on the same day *(62)*.

Equity

The Guideline Development Group considered that a revised recommendation would increase equity, since earlier ART (within two weeks) would be recommended for all people living with HIV regardless of CD4 count, including children.

Rationale for decision

The Guideline Development Group formulated a strong recommendation favouring starting ART as soon as possible within two weeks of initiating TB treatment, regardless of CD4 count, among adults based on low- to moderate-certainty evidence and a conditional recommendation for children and adolescents based on very-low-certainty evidence.

The Guideline Development Group acknowledged that the current use of less toxic HIV treatment options, such as DTG-based ART, reduces toxicity and drug–drug interactions (with appropriate adjustment of dosing with rifamycins), and the review results can be extrapolated to newer regimens.

Implementation considerations

People should be closely followed up to monitor adverse events related to co-treatment, immune reconstitution inflammatory syndrome, including paradoxical TB-associated immune reconstitution inflammatory syndrome, and other incident clinical events requiring prompt assessment and management, especially among children and pregnant or breastfeeding women. HIV programmes and service providers should establish mechanisms for adequate monitoring, including pharmacovigilance and surveillance for drug–drug interactions. Key considerations include adequate training of health-care personnel and programme managers to deliver integrated TB and HIV services (cross-training) and HIV and maternal, newborn and child health services, including for children, adolescents and pregnant women, co-location of services and establishing an integrated supply chain, laboratory and information systems.

Coordination between TB and HIV programmes to deliver these services is critical. Community engagement, patient education, engagement of adherence counsellors and social workers and peer support for early recognition of adverse events and to support retention and adherence to co-treatment are also needed. ART initiation among children with TB also needs parents to support adherence in the context of age-specific HIV disclosure and education regarding TB and HIV diagnosis and treatment *(71,72)*.

Research gaps

Research questions include addressing the safety and tolerability of earlier ART initiation among children, pregnant and breastfeeding women with HIV and TB and for people living with HIV who have drug-resistant TB. Overall, the long-term safety and tolerability of newer ARV drugs used in first-, second- or third-line regimens in the context of TB and HIV coinfection is also a critical gap More data are needed on the use of corticosteroids for people living with HIV who have low CD4 cell counts to prevent immune reconstitution inflammatory syndrome.

4.5.3 Timing of ART for people living with HIV and cryptococcal meningitis

Recommendation (2018)

Immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred by 4–6 weeks from the initiation of antifungal treatment *(strong recommendation, low-certainty evidence for adults and very-low-certainty evidence for children and adolescents).*

Source: *Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children (58).*

Rationale

WHO strongly recommends deferring ART initiation for four weeks following an amphotericin B–based induction regimen or 4–6 weeks following a fluconazole plus flucytosine induction regimen (based on a slower rate and longer time to achieve cerebrospinal fluid (CSF) fungal clearance with fluconazole versus amphotericin B) *(73)*. This recommendation applies across all age groups and also applies to ART-experienced people who develop cryptococcal meningitis following ART treatment failure who may need to switch to second-line ART and to people reinitiating after interruption. Although clear data are lacking, the consensus of the Guideline Development Group was that, for ART-experienced people, ART switches should be similarly deferred by four weeks following an amphotericin B–based induction regimen or 4–6 weeks following a fluconazole-based induction regimen.

No prospective evidence supports decisions about when to start ART among asymptomatic people with HIV and cryptococcal antigenaemia after initiation of pre-emptive antifungal therapy. Guidelines from the Southern African HIV Clinicians' Society recommend starting ART two weeks after starting fluconazole, and consideration is being given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis among people who test positive for whole-blood cryptococcal antigen *(22)*.

Implementation considerations

ART-experienced people who develop cryptococcal meningitis should be evaluated for potential underlying ART treatment failure, ideally through confirmation with an HIV viral load. ART switches should be deferred by four weeks following an amphotericin B–based induction regimen or 4–6 weeks following a fluconazole-based induction regimen.

Chapter 5 provides details on diagnosis, prevention and management of cryptococcal meningitis.

4.5.4 Timing of ART for people living with HIV and histoplasmosis

Recommendation (2020)

ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven *(conditional recommendation, very-low-certainty evidence).*

Source: *Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV (53).*

Background and rationale

Systematic review

The systematic review sought to compare the outcomes of early versus delayed initiation of ART among people with histoplasmosis. One randomized clinical trial with 282 participants met the inclusion criteria *(74)*. Based on limited evidence, the efficacy and safety outcomes of early versus late initiation of ART are unknown *(75)*.

Recommendation

ART should not be delayed for people diagnosed with disseminated histoplasmosis who are receiving antifungal therapy. The recommendation is conditional, with very-low-certainty evidence. The recommendation is based the low incidence of immune reconstitution inflammatory syndrome among people living with HIV receiving ART who have histoplasmosis *(76).*

This recommendation regarding the timing of ART only applies to people without central nervous system involvement, to avoid immune reconstitution syndrome in the central nervous system. Chapter 5 provides details on diagnosis, prevention and management of histoplasmosis.

4.6 What to start

4.6.1 First-line ART

Recommendations (2019)

First-line ARV drug regimen[a]

1. **DTG in combination with an NRTI backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART.[b]**
   - **Adults and adolescents[c]** *(strong recommendation, moderate-certainty evidence).*
   - **Infants and children with approved DTG dosing[d]** *(conditional recommendation, low-certainty evidence).*
2. **EFV at low dose (400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART[d]** *(strong recommendation, moderate-certainty evidence).*[e]
3. **A RAL-based regimen may be recommended as the preferred first-line regimen for neonates** *(conditional recommendation, very-low-certainty evidence).*

[a] See Table 4.3 for ARV drug selection.

[b] In settings or populations in which DTG is not accessible or unsuitable because of toxicity and national levels of pretreatment HIV drug resistance are ≥10%, PI/r-based ARV drugs should be used in first-line ART. The choice of PI/r will depend on the programmatic characteristics. Alternatively, and if feasible, HIV drug resistance testing can be considered to guide the selection of first-line ART regimen (see Section 4.9 and Table 4.3).

[c] See the section on women and adolescent girls of childbearing potential using DTG in this chapter.

[d] As of July 2021, the United States Food and Drug Administration and the European Medicines Agency have approved DTG for infants and children older than four weeks and weighing at least 3 kg.

[e] In settings in which pretreatment HIV drug resistance to NNRTIs is ≥10%, EFV-based ART should be avoided. EFV should also be avoided for people initiating or reinitiating first-line regimens with previous ARV drug exposure, regardless of the national prevalence of pretreatment drug resistance. See section 4.9 on HIV drug resistance considerations, Table 4.3 and Fig. 4.3.

Sources: *Policy brief: update of recommendations on first-and second-line antiretroviral regimens (77)* and *Guidelines on the public health response to pretreatment HIV drug resistance (78)*

Good practice statement (2017)

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and should promote the engagement and support of people and families to play an active role in their own care through informed decision-making. People should be encouraged but not coerced to start ART immediately and should be supported in making an informed choice regarding when to start ART and what ARV drug regimen to use.

Source: *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy, July 2017 (1).*

Background

WHO guidelines recommend earlier treatment initiation, using less toxic and more robust ARV drug regimens and simpler monitoring of the HIV treatment response. A key principle of recent WHO guidelines has been to harmonize ARV drug regimens across all populations by promoting drug options that are well studied and suited to children, adolescents, pregnant women, adults and people undergoing treatment of coinfections, notably TB *(3)*. WHO provided updated treatment recommendations in 2018 and 2019 and continues to closely follow the emerging evidence.

In 2018, WHO released interim guidelines providing updated guidance on the treatment and care of adults and adolescents living with HIV. The combination of TDF plus 3TC or FTC plus DTG was recommended as the preferred first-line regimen for adults and adolescents initiating treatment for HIV *(79)*. In addition, a combination of TDF + 3TC + EFV 400 mg was recommended as an alternative option for first-line ART in combination with TDF + 3TC for adults and adolescents. However, information on the efficacy of this regimen in subgroups, including pregnant women and people with HIV receiving TB co-treatment with a rifampicin-containing regimen, was lacking. In 2019, these guidelines were revised based on rapidly evolving evidence of safety, efficacy and programmatic experience using DTG and EFV 400 mg among pregnant women and people coinfected with TB *(80–82)*. Greater efficacy, better tolerability and availability of a once-daily fixed-dose combination were important factors for recommending DTG in first-line ART. However, a note of caution surrounding DTG for women of childbearing potential was issued following a signal of potential association between neural tube defects and DTG for women at the time of conception in an observational study from Botswana in 2018 *(83,84)*. These guidelines provided further reassurance of DTG as the preferred ARV drug in first-line ART because of the significant declining estimate of neural tube defects risk and observed efficacy *(77)*. High levels of pretreatment HIV drug resistance to NNRTIs among ART initiators have been reported from national surveys in low- and middle-income countries *(85)*. EFV-based ART is not recommended in settings in which levels of pretreatment drug resistance to NNRTIs are ≥10% *(78)*.

Consistent with broader efforts to improve toxicity profiles of first-line regimens, TAF was included as an option in special circumstances for adults with established osteoporosis and/or impaired kidney function and as an alternative option for children *(77)*. In many settings, HIV treatment for children is still often based on suboptimal ARV drug regimens and formulations.

Poor adherence because of lack of child-friendly formulations and continued use of NNRTI-based regimens despite the high levels of pretreatment HIV drug resistance to NNRTIs all contribute to lower rates of suppression of viral loads rates among children than among adults *(86–88)*. Partial or full approval for DTG, RAL and TAF for children has recently become available (see the annexes for dosing).

DTG has other advantages compared with EFV, including fewer drug interactions *(89)*, a higher genetic barrier to developing drug resistance *(90)* and activity against HIV-2 infection, which is naturally resistant to EFV *(91–93)*. The availability of DTG as a once-daily generic fixed-dose formulation at low price for most low- and middle-income countries also supports the recommended use of DTG as the preferred option for initiating ART *(94,95)*. Clinical and programmatic experience with DTG in low- and middle-income countries has progressively increased in recent years, but the long-term safety of DTG is still unknown and needs continued monitoring (see section on toxicity and weight gain).

Supporting evidence

DTG for adults and adolescents

An updated systematic review and network meta-analysis conducted in 2019 assessed the efficacy and safety of regimens based on DTG and EFV 400 mg among people living with HIV starting first-line ART *(66)*. The review found high- to moderate-certainty evidence that a regimen with two NRTIs plus DTG was more effective (with higher rates of suppression of viral loads and lower risk of treatment discontinuation and drug resistance development) than two NRTIs plus EFV for ART-naive adults. DTG was even more effective than two NRTIs plus EFV in populations with pretreatment resistance to EFV. Moderate-certainty evidence indicated better suppression of viral loads among people with a high initial viral load (>100 000 copies/mL) and lower risk of depression (grade 3/4), dizziness and treatment-related adverse events. However, there was an increased risk of weight gain (moderate-certainty evidence) and sleep disorders (low-certainty evidence). Regimens containing DTG and EFV were comparable with respect to mortality, suicide ideation and the occurrence of other nervous system and mental health events.

Identifying the most suitable ARV drug regimens for adolescents is important given the demonstrated higher risk of poor adherence, lower suppression of viral load, and higher risk of selecting multiclass resistance compared with adults *(96)*. In this context, a high value has been placed on more acceptable, tolerable and forgiving regimens for adolescents *(97)*. Due to limited evidence of the effectiveness of DTG versus EFV among adolescents, efficacy data were extrapolated from trials involving adults *(98)*. Most recently, findings from a randomized controlled trial *(99)* involving children and adolescents demonstrated the superiority of DTG-based regimens over NNRTI-based regimens for first-line ART. These findings are in accordance with findings for adults and strongly support WHO's existing recommendations.

DTG for pregnant and breastfeeding women and adolescent girls

Two randomized controlled trials investigated the use of DTG-based regimens among pregnant and breastfeeding women *(100,101)* and found DTG to be more effective than NNRTI-based regimens. The potential signal of neural tube defects for women of childbearing potential has been examined extensively; the risk is lower than initially observed and does not affect its use for women of childbearing potential. Section 4.8 summarizes the key pieces of evidence informing the current WHO recommendation *(77)*.

Box 4.2. A woman-centred approach

Woman-centred health services involve an approach to health care that consciously adopts the perspectives of women and their families and communities. This means that health services see women as active participants in and beneficiaries of trusted health systems that respond to women's needs, rights and preferences in humane and holistic ways (with no coercion). Care is provided in ways that respect a woman's autonomy in decision-making about her health, and services must provide information and options to enable women to make informed choices. The needs and perspectives of women and their families and communities are central to providing care and to designing and implementing programmes and services. A woman-centred approach is underpinned by two guiding principles: promoting human rights and gender equality.

A human rights-based approach to ART

All ART should be prescribed using a human rights–based approach. This means that women of childbearing potential or any pregnant or breastfeeding woman receives full information and medical guidance that is appropriate to her situation and is supported in making voluntary choices around medical therapy initiation, continuation and adherence or retention in care, as applicable. Health-care workers must help women to appropriately address their health-care needs and those of their children.

Source: *Consolidated guideline on sexual and reproductive health and rights of women living with HIV (102).*

Assessing the population-level benefits and risks of using DTG in first-line ART for women and adolescent girls of childbearing potential

In 2018, WHO convened a working group on modelling the population-level risks and benefits of women of childbearing potential initiating DTG-based ART. This group critically reviewed the structure, data inputs, policy scenarios and outcomes of existing models *(103,104)* and undertook a new analysis based on updated results on the relative effectiveness, toxicity and birth defects using DTG compared with other ARV drugs. A more comprehensive approach to outcomes included predicting the population-level effect of maternal death on child mortality overall as well as postnatal transmission through two years of age.

Both models predicted that, if women of childbearing potential start ART with DTG- versus EFV-based regimens, fewer women would die, fewer men would acquire HIV (decreased sexual transmission) and fewer children would acquire HIV (decreased vertical transmission). More infants would have neural tube defects with DTG versus EFV but overall fewer overall child deaths were predicted with DTG versus EFV because the decrease in the number of children dying from HIV-related causes overall because of lower vertical transmission is predicted to be greater than the increase in neural tube defects. DTG was also predicted to be more cost-effective, resulting in more disability-adjusted life-years (DALYs) averted at a lower cost than EFV. Using EFV for women of childbearing potential initiating ART rather than DTG would avert neural tube defects but would likely lead to other substantial negative effects on a population level (Fig. 4.1).

Fig. 4.1 Models of the potential benefits and harm with DTG versus EFV-based ART for women of childbearing potential

CEPAC: Tsepamo May 2019 neural tube defect risk, network meta-analysis of ARV efficacy, pretreatment drug resistance of 10.7%

For every neural tube defect averted by using **EFV versus DTG**, the following additional outcomes are predicted:



SYNTHESIS: Tsepamo May 2019 neural tube defect risk, including ADVANCE/NAMSAL, pretreatment drug resistance of 9%

For every adverse infant outcome (neural tube defects + neonatal deaths) averted by using **TLE versus TLD**, the following additional outcomes are predicted:



Numbers ≥0.5 rounded up.

Source: Dolutegravir Modelling Working Group.

These models were based on data from early 2019, which had higher estimated rates of neural tube defects. The models at the time concluded that the benefits of DTG for women of childbearing potential newly initiating ART (more maternal suppression of viral loads, fewer maternal deaths, fewer sexual transmissions and fewer mother-to-child transmissions) are likely to outweigh the risks (neural tube defects, morbidity and mortality among women of childbearing potential because of DTG-associated weight gain and neonatal deaths among the infants of pregnant women with DTG-associated weight gain). These benefits increase with rising levels of pretreatment HIV drug resistance to NNRTIs. Overall, these models indicate that DTG for women of childbearing potential newly initiating ART appears more cost effective than EFV in >85% of the setting scenarios. The additional evidence available after 2019 is expected to show that the benefits would further outweigh the risks.

DTG for neonates, infants and children

In nine national surveys among infants newly diagnosed with HIV in sub-Saharan Africa, pretreatment resistance to EFV and/or NVP ranged between 34% and 69% *(85)*. DTG overcomes the high level of pretreatment NNRTI resistance and provides a once-daily option with good tolerability and a good toxicity profile. The safety, tolerability, efficacy and favourable pharmacokinetics of DTG for infants and children from age four weeks to 12 years have been demonstrated through 48 weeks *(43–46)*. As of mid-2021, DTG was approved for infants and younger children by both the United States Food and Drug Administration and European Medicines Agency, in June 2020 and November 2020, respectively. Based on the validity of extrapolating efficacy data from trials involving adults when direct comparative efficacy evidence for children is not available, the 2018 Guideline Development Group agreed that DTG be recommended as the preferred first-line regimen for children for whom an approved DTG dosing exists (with the certainty of the evidence rated as low because it was extrapolated from studies involving adults). Considering the limited experience with DTG among children, WHO continues to advise that steps be taken to implement routine active toxicity monitoring according to WHO guidance *(2)*, but delays in implementing such monitoring should not delay scaling up DTG for children.

Most recently, an international multicentre randomized non-inferiority trial evaluating DTG + two NRTIs versus standard-of-care ART for children starting first- or second-line ART demonstrated the superiority of DTG-based regimens over the standard of care *(99)*.[5] A total of 707 children weighing at least 14 kg were enrolled in South Africa, Thailand, Uganda, Zimbabwe and Europe: 311 children started first-line ART (92% EFV among the standard of care) and 396 second-line ART (72% LPV/r and 25% ATV/r among the standard of care). After 96 weeks of follow-up, 14% of the DTG arm and 22% of the standard-of-care arm had experienced clinical or virological failure, a statistically significant difference of 8 percentage points. There was no difference in serious adverse events, but the children in the standard-of-care arm were more likely to need to modify their treatment regimen as a result of an adverse event. DTG-based ART was superior to standard-of-care ART based on treatment failure by 96 weeks among children and adolescents starting first- or second-line ART. An additional cohort of 85 children <14kg completed 96 weeks follow-up in June 2021. DTG-based ART was superior to SOC (predominantly PI-based) based on clinical/virological treatment failure by 96 weeks. The treatment benefit for DTG in the <14kg cohort was consistent with that observed in 707 children enrolled ≥14kg. In addition, suppressed VL <400c/ml was observed in 91% children <14kg randomised to DTG versus 71% in SOC at week 96 ($P = 0.03$). There were no safety concerns on DTG. The same trial investigated the dosing of DTG among children receiving rifampicin-containing TB treatment and found that doubling the dose of DTG could achieve appropriate DTG drug concentrations when co-administered with rifampicin and was safe and well tolerated *(105)*. Overall, these results support WHO recommendations and support full harmonization with adult treatment programmes. These findings will be considered in the future to reevaluate the strength of the existing recommendation.

Since DTG-based regimens are still being investigated for use in the first four weeks of life, RAL and NVP combined with a dual NRTI backbone are currently the only treatment options that can be used from birth. Comparative evidence between RAL and NVP is lacking for neonates, but based on data for adults, RAL in combination with an age-appropriate NRTI backbone is superior to an NVP-based regimen in terms of suppression of viral loads and CD4 cell count change (see section 7.13). The differences were not statistically significant for any other outcomes. The certainty of the evidence was rated as very low because the data were extrapolated from adults.

[5] Further resources on the ODYSSEY trial can be accessed here: https://odysseytrial.org/.

Despite its overall higher efficacy compared with the current standard of care in adults, RAL is known to have a lower genetic barrier to developing resistance compared with other INSTIs *(90,106).* There are concerns about the potential for suboptimal suppression of viral loads and the potential risk of selection for resistance to INSTIs in the context of a partially active NRTI backbone resulting from the presence of pretreatment resistance to NRTIs, which has been documented among up to 20% of ART-naive infant and young children *(88)*. In addition, the current recommendation for twice-daily administration of DTG after the failure of RAL-containing regimens makes using RAL less optimal in first-line ART unless no other effective options exist. For neonates, the lack of robust alternative options supports using RAL in first-line ART since the risk–benefit balance differs from that for its use for older infants and children, who can use solid LPV/r formulations. For these reasons, the 2018 Guideline Development Group concluded that RAL for neonates is preferred. It was noted that neonates starting ART with a RAL-based regimen should transition to DTG (see implementation considerations) as soon as possible to minimize selection for resistance to INSTIs.

DTG with TB co-treatment

Clinical data on the efficacy and safety of DTG co-administered with rifampicin among people with HIV-associated TB are currently based on pharmacokinetic studies involving healthy adult volunteers and the results of a single trial among adults with HIV receiving rifampicin-containing TB co-treatment *(107,108)*. These studies showed that the dose of DTG needs to be increased to 50 mg twice daily because of drug–drug interactions with rifampicin. The use of dose-adjusted DTG containing regimens was found to be effective during co-treatment for TB in terms of suppressing viral loads, time to suppress viral loads and improvement in CD4 cell counts. Furthermore, pharmacokinetic data from several DTG trials in TB-HIV co-infected patients suggest that DTG dose should remain twice a day for an additional two weeks after the last dose of rifampicin. It is recommended due to the enzyme inducing effect of rifampicin on DTG metabolism that slowly fades away after discontinuing the drug and can potentially increase the risk of DTG resistance development (see Annex 1) *(66,105,242)*. Low-certainty evidence indicated that DTG was either preferable or comparable to EFV in terms of the overall development of resistance, treatment discontinuation and severe adverse events. DTG had fewer discontinuations from adverse events, nervous system and mental health events, sleep disorders, dizziness and lower mortality compared with EFV (low-certainty evidence).

Pharmacokinetic studies are underway analysing the drug–drug interaction between DTG and other TB drugs among people with HIV-associated TB. Rifabutin and rifapentine can be safely co-administered with DTG at standard doses for people living with HIV *(108)*. The DOLPHIN trial was a Phase 1/2, single-arm trial in which participants received 50 mg of daily DTG and once-weekly rifapentine (900 mg) or isoniazid (900 mg) for 12 weeks. The primary endpoints were adverse events (grade 3 or higher) and DTG population pharmacokinetics, assessed among participants. The results suggest that 12 doses of once-weekly rifapentine–isoniazid can be given for TB prophylaxis to people living with HIV taking DTG-based ART without dose adjustments. Further exploration of the pharmacokinetics, safety and efficacy for children and pharmacodynamics for individuals naive to ART is needed *(108,109)*. The data on using DTG with rifabutin comes from a single Phase 1 healthy volunteer study (n = 12). The overall plasma concentrations of DTG were similar when DTG was given with or without rifabutin, and no DTG dose adjustment was required.

Use of EFV 400 mg in adults and adolescents

The efficacy of EFV 400 mg compared with EFV 600 mg as part of first-line therapy was reviewed *(66)*. EFV 400 mg was considered a candidate for first-line ART since it was potentially a more tolerable option than EFV 600 mg for people who are unable or unwilling to initiate ART with DTG. In accordance with the WHO 2019 systematic review to inform the guidelines, EFV 400 mg is expected to be similar to EFV 600 mg, with some additional advantages in terms of tolerability, smaller pill size and reduced nervous system and mental health events. EFV 400 mg is expected to be safe for use in pregnancy and may also be administered during treatment of HIV-associated TB *(77)*.

EFV-based ART should be avoided in the following scenarios: (1) countries in which the prevalence of pretreatment HIV drug resistance to NNRTIs among people initiating first-line ART is equal or greater than 10% based on national HIV drug resistance surveys; and (2) in populations initiating ART reporting previous exposure to NNRTIs regardless of national HIV drug resistance prevalence data because of a high risk of HIV drug resistance in this group *(78,110)*.

TAF for adults, adolescents and children

TAF is a prodrug of tenofovir, available as a single-strength tablet and in combination with FTC and DTG or other INSTIs. Studies have suggested improved renal and bone safety markers compared with TDF.

A systematic review found that, compared with TDF, TAF leads to less impact on spine and hipbone mineral density and renal function markers *(77)*. Clinical renal and bone events were rare with both drugs, and they did not differ in suppressing viral loads *(62)*. Additional benefits of TAF over TDF include small pill size and potential cost savings. However, the systematic review also found evidence that people taking TAF experienced a rise in cholesterol levels and body weight gain *(62,111).* The long-term safety of TAF is unknown. Another limitation with TAF is its interaction with rifampicin and other common anti-TB drugs, and the correct dose to administer during TB co-treatment has not been established *(112)*. There is also limited information on safety and efficacy in important subpopulations, including pregnant women *(113)*. To date, pharmacological studies have demonstrated acceptable TAF plasma concentrations in pregnancy *(114)*, but more data are needed to establish safety in pregnancy.

The evidence base for TAF for children and adolescents is limited to safety and pharmacokinetic data using adult dosing in weight bands above 25 kg *(115,116)*. Limited data are available for children 14 to <25 kg and older than two years using a low dose of FTC + TAF 120/15 mg with a boosted third agent *(117,118)*. Bone and renal safety and suppression of viral loads were all favourable. The acceptability and palatability of low-dose formulations containing TAF have also been demonstrated in this age group *(119)*. In this context, the Guideline Development Group decided to make no recommendation on using TAF as a preferred NRTI for first-line regimens across age groups and to maintain TDF as the preferred ARV drug to combine with DTG and 3TC (or FTC). The current WHO-recommended backbone is TDF + 3TC for adults and adolescents and ABC + 3TC for children and infants. Nevertheless, TAF was considered a favourable option for special circumstances when bone and renal toxicity are a particular concern (such as the presence of osteoporosis or mild chronic renal disease and concomitant use of nephrotoxic drugs) for adults *(120,121)*.

For children, TAF was considered a desirable option in the context of limited NRTI options available and the concerns about using TDF because of bone toxicity risk. Other considerations favouring TAF for children include an improved resistance profile (versus ABC and AZT), activity against HBV infection and regimen harmonization if TAF is used for adults and adolescents. However, long-term safety is unknown, and currently available evidence for using TAF among children is only available when administered with an unboosted third agent. TAF in this context is considered an appropriate alternative option to be used within unboosted ARV drug regimens in first-, second- or third-line ART.

Table 4.3 Preferred and alternative first-line ART regimens for adults, adolescents, children and neonates

Populations	Preferred first-line regimen	Alternative first-line regimen	Special circumstances
Adults and adolescents	TDF + 3TC (or FTC) + DTG[a,b]	TDF + 3TC + EFV 400 mg[b]	TDF + 3TC (or FTC) + EFV 600 mg[b] AZT + 3TC + EFV 600 mg[b] TDF + 3TC (or FTC) + PI/r[b] TDF + 3TC (or FTC) + RAL TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + DTG[a] TDF + 3TC (or FTC) + PI/r[b]
Children	ABC + 3TC + DTG[d]	ABC + 3TC + LPV/r TAF[e] + 3TC (or FTC) + DTG	ABC + 3TC + EFV (or NVP) ABC + 3TC + RAL[f] AZT + 3TC + EFV[g] (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates	AZT (or ABC) + 3TC + RAL[h]	AZT + 3TC + NVP	AZT + 3TC + LPV/r[i]

[a] Section 4.8 discusses toxicity considerations for pregnant and breastfeeding women.

[b] EFV-based ART should not be used in settings with national estimates of pretreatment resistance to EFV of 10% or higher. In settings with high HIV drug resistance prevalence and where DTG is unavailable or unsuitable due to toxicity, a boosted PI-based regimen should be used. The choice of PI/r will depend on programmatic characteristics. Alternatively, HIV drug resistance testing should be considered, where feasible, to guide first-line regimen selection (see section 4.9).

[c] TAF may be considered for people with established osteoporosis and/or impaired kidney function.

[d] For age and weight groups with approved DTG dosing, from four weeks and 3 kg.

[e] For age and weight groups with approved TAF dosing.

[f] RAL can be used as an alternative regimen only if LPV/r solid formulations are not available.

[g] EFV should not be used for children younger than three years of age.

[h] Neonates starting ART with a RAL-based regimen should transition to DTG as soon as possible. This guideline provides new dosing guidance (see the annexes for dosing) for ABC for neonates. However, due to limited availability of ABC syrup, AZT syrup remains an effective option to combine with 3TC for the first four weeks of life.

[i] LPV/r syrup or granules can be used if starting after two weeks of age.

Cost and cost–effectiveness, equity, acceptability and feasibility

In 2019, the Guideline Development Group examined the costs, cost–effectiveness, equity, acceptability and feasibility. The conclusions drawn from the Guideline Development Group meeting were that a DTG-based regimen was a highly cost-effective option, feasible, acceptable and equitable. Since this recommendation was developed, DTG uptake has greatly expanded, and further formulations such as dispersible tablets for children have been approved and are expected to become increasingly available.

Clinical and implementation considerations

Despite a lower risk of drug–drug interactions compared with NNRTIs and boosted PIs, DTG cannot be used with some anticonvulsant drugs (such as phenytoin) and antiarrhythmic drugs (such as dofetilide). DTG cannot be simultaneously administered with cation-

containing products as antacids (such as calcium and magnesium), laxatives and multivitamin supplements because of the risk of chelation resulting in subtherapeutic DTG blood levels. If combined, DTG should be administered two hours before or six hours after taking medicines containing polyvalent cations *(122)*. This guidance applies equally to all populations and is especially relevant for pregnant women and children, who frequently receive vitamin supplementation (see Annex 2).

Treating neonates requires testing and linkage to care in the first four weeks of life. In settings where this is possible, using RAL granules is expected to be feasible, as demonstrated in a rapid assessment undertaken in KwaZulu-Natal, South Africa *(96).*

People with HIV-associated TB infection and treated with rifampicin-containing regimens should receive an additional 50 mg of DTG 12 hours after taking their main ARV drug regimen.

Transition to optimal ARV drug regimens for children

Given the suboptimal viral load suppression on NNRTI-based regimens as demonstrated by increasing evidence from programmatic and observational data *(123)*, NNRTI-based regimens are discouraged now that alternatives are available. DTG-based regimens provide a more efficacious and tolerated option that overcomes potential resistance to NNRTIs and provides the opportunity to fully harmonize regimens across children and adults.

The WHO-convened Paediatric ARV Working Group strongly encourages HIV programmes to rapidly implement current WHO recommendations *(77)* for DTG-based regimens for first-line ART, now able to be implemented for all infants and children older than four weeks and weighing at least 3 kg, as approved by the United States Food and Drug Administration *(124)* and the European Medicines Agency *(125)*. Additional support for current WHO recommendations has recently come from the ODYSSEY trial, which demonstrated superior viral outcomes among children randomized to DTG-based first- or second-line ART compared with standard care *(99)*.

Previous versions of WHO guidelines considered how to optimize treatment regimens as children grow and better combinations or formulations are available to them *(126)*. This may enable access to more potent regimens that prolong the duration of first- or second-line ART and support adherence with once-daily administration or lower pill count. In March 2021, the WHO-convened Paediatric ARV Working Group was asked to carefully consider the benefits and risks related to a programmatic transition to DTG-based regimens for children established on first- and second-line ART (if older than four weeks and weighing at least 3 kg), acknowledging the current evidence gaps and anticipated benefits for children living with HIV and for HIV programmes.

The Working Group noted the anticipated individual (palatability, potency, ease of administration, once-daily administration and drug–drug interaction profile) and programmatic (cost, simplification and consolidation of demand and procurement) benefits of a programmatic transition to DTG-based regimens for infants and children who are currently established on first-line ART (if older than four weeks and weighing at least 3 kg).

The Working Group also acknowledged the lack of direct evidence supporting use of DTG-based regimens with a partly active NRTI backbone (some level of resistance to one or both NRTIs) for infants and children <20 kg. However, programmatic experience *(127,128)* shows good suppression of viral loads for children >20 kg established on ART and transitioning to DTG-based regimens, and recent randomized controlled data for adults show similar findings *(129)*, supporting the use of DTG-based regimens for people with a partly active NRTI backbone.

As a result, the Paediatric ARV Working Group encourages rapid transition to DTG-based regimens for all infants and children (older than four weeks and weighing at least 3 kg) established on first-line ART regardless of their current regimen.[6] The timing of transition to a DTG-based regimen for these infants and children should account for:

- the availability and anticipated supply of DTG dispersible tablets and, in case of inadequate supplies to provide DTG to all children, the need to give priority to the children who most need DTG (once the first- and second-line need has been addressed):
  - children receiving NNRTI-based regimens;
  - children who need to start TB treatment;
  - children receiving LPV/r solid formulations, especially if they continue to present challenges in administration and/or challenges with attaining optimal viral load suppression; and
- viral load testing should not be considered a precondition to undertaking programmatic or individual transition to DTG-based regimens: although viral load monitoring remains a good practice to deliver appropriate care to children living with HIV, infants and children should not have their transition to DTG delayed because of lack of documented viral load.

Table 4.4 Transition to optimal ARV drug regimens for children who are established on ART[a]

Current regimen	Weight	Optimal regimen for transition	Considerations
AZT + 3TC + NVP AZT + 3TC + EFV	<30 kg	ABC + 3TC plus DTG	As long as above 3 kg and four weeks old
ABC + 3TC + NVP **ABC + 3TC + EFV** **ABC + 3TC + LPV/r** **AZT + 3TC + LPV/r**	>30 kg	TLD	-

[a] See Chapter 7 for definition of being established on ART.

The group also agreed that DTG dose adjustment during rifampicin-containing TB treatment should align with approval by the United States Food and Drug Administration and support the use of DTG twice a day across age groups and weight bands. Table 4.5 provides more details on TB co-treatment.

Finally, the Paediatric ARV Working Group reviewed administration guidance and agreed that DTG dispersible tablets should be ideally dispersed in water or swallowed whole. Based on limited data, crushing, chewing or mixing with other foods or liquids (breast-milk) can be considered as long as the entire recommended volume is ingested.

When RAL granules are used to start treatment among neonates diagnosed with HIV, careful consideration should be given to making the appropriate RAL dose change after the first week of life and then again after four weeks (see Annex 1), when transition to DTG 10 mg scored dispersible tablets (without viral load testing) is strongly advised. Ensuring adequate training of health-care workers to instruct caregivers remains critical because of the challenges of correctly reconstituting and administering the RAL granule formulation.

[6] For children on RAL-based regimens, viral load testing should be undertaken before transitioning to DTG.

Table 4.5 Guidance for adjusting ART when rifampicin-based TB treatment starts

	ART regimen	What to do when TB treatment is started
Neonates	RAL-based[a]	Dose adjustment needed: see the annexes for ARV dosing
	NVP-based	Change of regimen needed: NVP to be replaced as soon as possible with DTG or LPV/r (with appropriate dose adjustment)
Children	DTG-based regimen[a]	Dose adjustment needed: see the annexes for ARV dosing
	LPV/r-based regimen	Transition to DTG-based regimen (with appropriate dose adjustment) is preferable, and if not possible, LPV/r dose adjustment is needed: see the annexes for ARV dosing
	RAL-based regimen	Transition to DTG-based regimen (with appropriate dose adjustment) is preferable, and if not possible, RAL dose adjustment is needed: see the annexes for ARV dosing
	TAF-containing regimen	Change of regimen needed: TAF to be replaced by ABC or TDF
	ATV/r-based regimen	Change of regimen needed: replace ATV/r with DTG if DTG naive, with LPV/r if DTG experienced
	DRV/r-based regimen	Change of regimen needed: replace DRVr with DTG if DTG naive, with LPV/r if DTG experienced

[a] Preferred for ART initiation while receiving TB treatment.

ART transition for adults and adolescents

An important consideration is the issue of changing to a DTG-based regimen for people who are established on first-line NNRTI-containing regimen (see Table 4.6). Routine viral load monitoring should be encouraged as good practice. Programmes should consider ART transition an opportunity to emphasize treatment adherence counselling and support. If countries adopt ARV drug substitution in the absence of viral load testing, closely monitoring population-level viral load and drug resistance surveillance are encouraged. See specific scenarios in Table 4.6.

Considerations for replacing EFV-based first-line regimens with DTG-based regimens while maintaining the same NRTI backbone

People established on TDF + 3TC (or FTC) + NNRTI regimens (no evidence of clinical or immune failure) with documented suppression of viral loads should be assessed, since an ARV switch may confer new side-effects and potentially interfere with adherence *(130)*. However, DTG regimens may be more durable in the long term. Substitutions should also be considered carefully in the context of drug supply and the user's choice (see Tables 4.2 and 4.3).

For people who are clinically or immunologically stable but have no documented viral load test results, replacing TDF + 3TC (or FTC) + NNRTI with TDF + 3TC + DTG may place them at risk of suboptimal therapy because of an inactive NRTI backbone in some instances. Dual resistance to 3TC or FTC and TDF is common and is estimated to be present in about 60% of individuals for whom NNRTI-based ART has failed *(131)*.

Viral load monitoring before substituting from TDF + 3TC (or FTC) + NNRTI to TDF + 3TC + DTG is recommended as the preferred approach. If countries adopt this substitution in the absence of viral load testing, closely monitoring population-level viral load levels and drug resistance outcomes at the population level is encouraged.

Following the development of the updated WHO ARV drug recommendations in 2019, the recent conclusions from the NADIA trial *(129)* were that DTG with two NRTIs highly effectively suppresses viral loads up to 48 weeks, even among people many of whom have extensive NRTI resistance and no predicted activity of the prescribed dual NRTI backbone and that tenofovir can be maintained in second-line therapy without switching to AZT, with advantages for users and programmes. These results are reassuring in settings with limited access to viral load tests where transition to TLD might occur without a viral load test. This approach is also supported by the recent WHO think-tank on ARV drug optimization *(132)*, with experts voicing support for transitioning to DTG-based ART without previous viral load if the person is established on ART.

Table 4.6 Consideration for transition to TLD among adults and adolescents

Treatment transition scenario	Preferred approach	Comments
DTG for people living with HIV already using a first-line regimen		
Clinical or immunological failure or viral load non-suppressed (viral load >1000 copies/mL)	Switch to AZT + 3TC + DTG[a]	• Consideration may be given to retaining TDF + 3TC given the advantages of TDF over AZT and recent data demonstrating that suppression of viral loads can be achieved through this approach *(129)*. More data are anticipated • Provide adherence support
Viral load suppressed (<1000 copies/mL)	Substitution to a TLD regimen may be considered in accordance with national recommendations	• Substitution should be considered in the context of drug supply and patient choice. Substitution may confer new side-effects and interfere with adherence *(130)*. However, DTG regimens may be more durable in the long term.
Clinically and immunologically established on ART[b] and viral load unknown	Give priority to viral load testing if possible or consider other programmatic or clinical indications for decision-making, and substitution to a TLD regimen may be considered	• Lack of viral load should not be a barrier to transition. – Recent evidence is reassuring on the effectiveness of DTG with inactive or partly active NRTI backbone – Important in settings with >10% pretreatment NNRTI resistance
Established[b] on suboptimal first-line ARV regimens	Switch to TLD	

[a] After adherence check and persistent detectable viral load.
[b] Chapter 7 defines being established on ART.

Research gaps

Research on using ART in the subpopulation of individuals with hepatitis B and C requiring co-treatment is needed.

Future research is required on DTG-associated weight gain, stratified by baseline viral load level, to better understand the pattern of fat deposition, on how people value the weight gain, the geographical and population differences by differing dietary patterns and the long-term clinical consequences of DTG-related weight gain.

Better understanding of the pharmacokinetics and appropriate dosing of DTG in neonates is needed as well as data on the short- and long-term safety of DTG-based regimens.

More evidence is also required to assess the levels of suppression of viral loads in programmatic settings when DTG or RAL-based ART regimens are used across populations in first-line ART, the effectiveness of DTG when used in association with a compromised NRTI backbone and the potential impact of polymorphic mutations on DTG efficacy *(133)*.

Long-term information on suppression of viral loads among people using formulations containing EFV 400 mg, especially among pregnant women and individuals requiring TB co-treatment, particularly including rifampicin, are needed.

In addition, the pharmacokinetics and safety of alternative dosing of TAF when used during TB co-treatment need to be better understood. Data are needed on pharmacokinetics and appropriate dosing of TAF for children weighing less than 25 kg in the context of boosted and unboosted regimens.

4.6.2 Second-line ART

Recommendations (2019)

Second-line ARV drug regimens[a]

- **DTG in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG-based regimens are failing.**
  - **Adults and adolescents**[b] *(conditional recommendation, moderate-certainty evidence)*
  - **Children with approved DTG dosing** *(conditional recommendation, low-certainty evidence)*
- **Boosted protease inhibitors in combination with an optimized nucleoside reverse-transcriptase inhibitor backbone are recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing** *(strong recommendation, moderate-certainty evidence).*

[a] See Table 4.4 for ARV drug selection.

[b] See Box 4.7 on women and adolescent girls of childbearing potential using DTG.

Source: *Update of recommendations on first- and second-line antiretroviral regimens (77).*

Background

WHO continues to promote optimization and sequencing from first-line to second-line regimens to reduce toxicity and pill burden, ensure once-daily dosing, ensure minimal or no cross-class resistance and with a preference for regimens that can be used across populations *(134,135)*. Several studies exploring various strategies for second-line ART have been conducted recently, including those focusing on using ART classes other than PIs and NRTIs, NRTI-sparing regimens and strategies for optimizing PI doses *(136,137)*.

The availability of new ARV drugs with potential lower toxicity and higher efficacy (such as DTG) can impact the future recommendations on ART sequencing and the expectations about clinical and societal treatment benefits (life expectancy and quality of life) and durability of anti-HIV regimens.

The choice of NRTI backbone for second-line ART continues to be determined by which NRTI was used in first-line ART – if ABC + 3TC or TDF + 3TC (or FTC) were used, AZT + 3TC should be used in second-line ART and vice versa – with the goal of optimizing sequencing in the context of lack of access to genotyping, with recent evidence showing that AZT is not better than TDF in the context of the failure of a TLE regimen *(129)*.

More robust second-line options are needed for children among whom rates of suppressed viral loads on ART have been consistently lower than among adults, especially among children younger than five years (98,138). Despite major advances in ARV drug development for adults, treatment for children often relies on suboptimal drug regimens and formulations. Except for LPV/r, co-formulated boosted PIs are still unavailable, and developing a coformulation of DRV/r for children is a priority (139).

Access to viral load monitoring continues to be limited in many countries, and this presents important challenges to timely switching to second-line regimens. Data on the use of ATV/r-, DRV/r- and LPV/r + RAL-based regimens continue to be limited, as evidenced by the updated systematic review.

Supporting evidence

DTG for adults and adolescents

The WHO 2018 interim guidelines recommended two NRTIs + DTG for people for whom a first-line regimen has failed, with the note of caution on using DTG for women of childbearing potential. The updated systematic review provided substantially more data on LPV/r-based second-line ART compared with LPV/r + RAL, DRV/r and ATV/r-based regimens. High-certainty evidence indicated that a DTG-based second-line regimen had better and faster suppression of viral loads compared with an LPV/r-based regimen, low-certainty evidence indicated that it was better than an LPV/r + RAL regimen and moderate-certainty evidence indicated that it was better than a DRV/r-based regimen in terms of efficacy, based on the network meta-analysis.

Moderate- to high-certainty evidence indicated that a DTG-based second-line regimen would lead to fewer discontinuations and treatment-related adverse effects than an LPV/r-based regimen, and low- to very-low-certainty evidence indicated that it was comparable or better than an LPV/r + RAL-based regimen. No direct comparisons were possible with a DRV/r-based regimen because of lack of studies. Low- to moderate-certainty evidence indicated that DTG-based second-line ART would have fewer nervous system and mental health adverse events, and low-certainty evidence indicated a reduced or equivalent development of resistance in second-line ART compared with PIs.

DTG has other advantages compared with other second-line options, including lower cost, better tolerability, less potential for drug–drug interactions and lower pill burden.

Experience with DTG in low- and middle-income countries as second-line therapy is very limited compared with LPV/r and other boosted PIs, with more than 60% of people living with HIV in low- and middle-income countries receiving an LPV/r-based second-line regimen. There are also concerns about complexity related to the need to double-dose DTG in the presence of rifampicin, as for first-line therapy.

DTG in pregnancy as second-line ART has not been separately evaluated, but the review of safety and tolerability of DTG use in pregnancy has been detailed in the updated systematic review for first-line regimens.

All PIs have known side-effects (see section 4.8). A systematic review found evidence that PI use in pregnancy, especially LPV/r, is associated with more negative pregnancy outcomes, including preterm or very preterm birth and small or very small for gestational age compared with DTG or EFV. An increase in dose in late pregnancy may be needed for ATV/r and LPV/r, since a decline in drug levels is observed, but this may be associated with decreased tolerability. Although adverse pregnancy outcomes may be increased with PIs compared with EFV or DTG, the available data showed similar rates of stillbirth, miscarriage, low or very low birth weight, small or very small for gestational age and birth defects when comparing ATV/r, DRV/r and LPV/r within the PI class.

The interactions between LPV and rifampicin are well known, with reduced levels of LPV during TB co-treatment. A recent study of LPV/r super-boosting (to achieve a 1:1 ratio rather than the standard 4:1) among young children living with HIV receiving rifampicin-containing TB treatment compared with LPV/r without rifampicin found that, although LPV exposure was non-inferior, acceptability was poor *(140)*. Other studies of double-dosing standard LPV/r regimens (as opposed to super-boosting) during TB co-treatment among young children have also shown this combination to be effective and well tolerated *(141,142)*. A study of the pharmacokinetics and safety of adjusted DRV/r with rifampicin was stopped because of hepatotoxicity after 17 of the planned 28 people living with HIV enrolled and started treatment *(143).* Pharmacokinetic studies of a combination of ATV and rifampicin have shown decreased ATV levels, and this combination is not recommended. Studies with rifapentine and PIs are not available *(144)*.

Limited evidence from a recent clinical trial *(129)* supports using DTG in combination with TDF and 3TC as second-line ART for people for whom TDF + 3TC (or FTC) + EFV is failing as a first-line regimen. The use of DTG in combination with an optimized NRTI backbone is preferable and recommended as good practice: AZT + 3TC should be used as the NRTI backbone in a second-line regimen if ABC + 3TC or TDF + 3TC (or FTC) was used in the failing first-line regimen and vice versa (see Table 4.7 and Box 4.3). WHO continues to monitor emerging evidence in relation to retaining TDF + 3TC when transitioning to second-line regimens.

After the recommendations for second-line ART were updated in 2019, a multicountry prospective study *(145)* (THILAO-ANRS-12269) followed up adults with known treatment failure to a boosted PI regimen, with nine adherence interventions and reported outcomes at 64 weeks. Of 198 participants, 6 died before the study period ended, with 130 achieving suppression of viral loads (67%) and continuing with second-line ART and 63 (33%) switching to a third-line regimen at week 16. The study reinforces the need for adherence counselling and the need to transition to third-line regimens in a timely manner, noting that lack of availability of genotypic resistance testing should not be a barrier to transitioning to third-line ART.

DTG in second-line regimens for children and infants

Since 2016, the Paediatric Antiretroviral Drug Optimization group has endorsed the rapid introduction of INSTIs for infants and children, with a preference for DTG over RAL. The group has also supported using DTG in first- and second-line ART and promoted the extrapolation of efficacy data from trials involving adults when direct comparative evidence is not available for children *(98)*. Although using DTG as second-line ART for children was still being evaluated, based on extrapolation from data for adults, the 2018 Guideline Development Group agreed that DTG in combination with an optimized backbone regimen may be recommended as a preferred second-line regimen for all children for whom an approved DTG dosing is available and that routine clinical monitoring for toxicity should be ensured when this recommendation is implemented.

Most recently, an international multicentre randomized non-inferiority trial evaluating DTG + two NRTIs versus the standard of care for children starting first- or second-line ART demonstrated the superiority of DTG-based regimens over the standard of care *(99).* A total of 707 children weighing at least 14 kg were enrolled in South Africa, Thailand, Uganda, Zimbabwe and Europe: 311 children started first-line ART (92% EFV among the standard of care) and 396 second-line ART (72% LPV/r and 25% ATV/r among the standard of care). After 96 weeks of follow-up, 14% of the DTG arm and 22% of the standard-of-care arm had experienced clinical or virological failure, a statistically significant difference of 8 percentage points. There was no difference in serious adverse events, but the children in the standard-of-care arm were more likely to need to modify their treatment regimen as a result of an adverse event. DTG-based ART was superior to standard-of-care ART based on treatment failure by 96 weeks among children and adolescents starting first- or second-line ART. Overall, these results support the 2018 WHO guideline recommendations and support full harmonization with adult treatment programmes. Given these findings, WHO will consider the need to revise the strength of the recommendation in the near future.

For children for whom DTG is not available, boosted PI- and RAL-based regimens continue to be preferred for children for whom an NNRTI- or PI-based first-line regimen is failing, respectively *(3).*

In March 2021, the WHO-convened Paediatric ARV Working Group was asked to carefully consider the benefits and risks related to a programmatic transition to DTG-based regimens for children established on first- and second-line ART (if older than four weeks and weighing at least 3 kg), acknowledging the current evidence gaps and anticipated benefits for children living with HIV and for HIV programmes. The Working Group noted the anticipated individual (palatability, potency, ease of administration, once-daily administration and drug–drug interaction profile) and programmatic (cost, simplification and consolidation of demand and procurement) benefits of a programmatic transition to DTG-based regimens for infants and children who are established on first-line ART (if older than four weeks and weighing at least 3 kg). The Working Group also acknowledge the lack of direct evidence supporting use of DTG-based regimens with partly active NRTI backbone (some level of resistance to one or both NRTIs) for infants and children weighing less than 20 kg. However, programmatic experience *(127,128)* shows good suppression of viral loads among children established on ART weighing more than 20 kg transitioning to DTG-based regimens, and recent randomized controlled data for adults *(129)* supports using DTG-based regimens for people with partly active NRTI backbone.

The Paediatric ARV Working Group offered considerations for both first- and second-line regimens, which are described below and included in the consideration for first-line ART.

As a result, the Paediatric ARV Working Group encourages rapid transition to DTG-based regimens for all infants and children (older than four weeks and weighing at least 3 kg) established on second-line ART regardless of their current regimen. The timing of transition to a DTG-based regimen for these infants and children should account for:

- the availability and anticipated supply of DTG dispersible tablets and, in case of inadequate supplies to provide DTG to all children, the need to give priority to the children who most need DTG (once the first- and second-line need has been addressed):
  - children receiving NNRTI-based regimens;
  - children who need to start TB treatment;
  - children receiving LPV/r solid formulations, especially if they continue to present challenges in administration and/or challenges with attaining optimal viral load suppression;
- viral load testing should not be considered a precondition to undertaking programmatic or individual transition to DTG-based regimens: although viral load monitoring remains a good practice to deliver appropriate care to children living with HIV, infants and children should not have their transition to DTG delayed because of lack of documented viral load; and
- for children receiving RAL-based regimens, viral load testing should be undertaken before transitioning to DTG.

Table 4.7 Preferred and alternative second-line ART regimens for adults, adolescents, children and infants

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents[a]	TDF[b] + 3TC (or FTC) + DTG[c]	AZT+ 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r[d]
	TDF + 3TC (or FTC) + EFV (or NVP)	AZT +3TC + DTG[c]	AZT + 3TC + ATV/r (or LPV/r or DRV/r)[d]
	AZT + 3TC +EFV (or NVP)	TDF[b] + 3TC (or FTC) + DTG[c]	TDF[b] + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)[d]
Children and infants	ABC + 3TC + DTG[e]	AZT+ 3TC + LPV/r (or ATV/rf)	AZT +3TC + DRV/r[g]
	ABC (or AZT) +3TC + LPV/r	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[e]	AZT (or ABC) +3TC + LPV/r (or ATV/r[f])
	AZT + 3TC + NVP	ABC + 3TC + DTG[e]	ABC + 3TC + LPV/r (or ATV/r[f])

[a] Sequencing if a PI is used in first-line ART: TDF + 3TC (or FTC) + ATV/r (or LPV/r, or DRV/r, depending on programmatic considerations) in first-line ART should be sequenced to AZT + 3TC + DTG in second-line ART.

[b] See Box 4.3.

[c] TAF can be used as an alternative NRTI for children and in special situations for adults (see section on TAF in first-line ART).

[d] RAL + LPV/r can be used as an alternative second-line regimen for adults and adolescents.

[e] As of July 2021, the United States Food and Drug Administration and the European Medicines Agency have approved DTG for infants and children older than four weeks and weighing at least 3 kg.

[f] ATV/r can be used as an alternative to LPV/r for children older than three months, but the limited availability of suitable formulations for children younger than six years, the lack of a fixed-dose formulation and the need for separate administration of the RTV booster should be considered when choosing this regimen.

[g] DRV/r should not be used for children younger than three years and should be combined with appropriate dosing of RTV (see the annexes).

Table 4.8 outlines situations in which using genotypic resistance testing may be considered.

Table 4.8 Summary of sequencing options for first-line, second-line and third-line ART regimens and preferred and alternative first-line regimens for adults, adolescents and children

Populations	First-line regimen	Second-line regimen	Third-line regimen
Adults and adolescents	Two NRTIs + DTG	Two NRTIs + ATV/r (or LPV/r)	DRV/r[a] + 1–2 NRTIs ± DTG[b] Optimize the regimen using a genotype profile (if LPV is used in second-line ART)
		Two NRTIs + DRV/r	Optimize the regimen using a genotype profile
	Two NRTIs + EFV	Two NRTIs + DTG	Two NRTIs + (ATV/r, DRV/r or LPV/r) ± DTG[b]
Children	Two NRTIs + DTG	Two NRTIs + LPV/r (or ATV/r[c])	DRV/r[a,d] + 1–2 NRTIs ± DTG[b,e] Optimize the regimen using a genotype profile for children younger than three years
	Two NRTIs + LPV/r	Two NRTIs + DTG	DRV/r[a,d] + 1–2 NRTIs ± DTG[b,e] Optimize the regimen using a genotype profile for children younger than three years
	Two NRTIs + NNRTI	Two NRTIs + DTG	Two NRTIs + (ATV/r, LPV/r or DRV/r[d]) ± DTG[e]

[a] 600/100 mg twice daily.
[b] 50 mg twice daily.
[c] Boosted PI.
[d] DRV cannot be used for children younger than three years.
[e] For age and weight groups with approved DTG dosing (<20 kg).

Rationale for the recommendation

The Guideline Development Group considered the costs, cost–effectiveness, acceptability, feasibility and equity and concluded that a DTG-based regimen is equitable, acceptable, feasible and a cost-effective option *(77,79).*

Box 4.3. Using TDF + 3TC + DTG in second-line ART following failure of TDF + 3TC (or FTC) + EFV: HIV drug resistance considerations

Using DTG in combination with an optimized NRTI backbone is preferable and recommended as good practice (AZT + 3TC should be used as the NRTI backbone in a second-line regimen if TDF + 3TC (or FTC) was used in the failing first-line regimen and vice versa). Although using TDF + 3TC (or FTC) + DTG in second-line ART following the failure of TDF + 3TC (or FTC) + EFV may have programmatic advantages, it also raises concerns about the potential use of a suboptimal therapy. Viral resistance to TDF and 3TC is common among people for whom NNRTI-based ART is failing; up to two thirds of individuals have viral resistance to TDF, and the vast majority have resistance to 3TC *(85).*

There is currently limited evidence on the efficacy of DTG in combination with an NRTI backbone whose activity is compromised by the presence of major NRTI resistance-associated mutations; DTG in combination with an optimized backbone is therefore recommended.

In the DAWNING study, people were switched from NNRTI- to DTG-based ART with at least one active NRTI predicted by genotypic resistance testing. Although DTG seems to be effective with at least one active NRTI for people for whom NNRTI-based ART is failing, a retrospective analysis suggests that selecting NRTI backbone sequencing according to WHO guidelines achieved modest but significantly greater suppression of viral loads *(98)*.

Further, DTG has not been directly evaluated in combination with an NRTI backbone that is predicted to be inactive by genotypic resistance testing, but the findings from DTG monotherapy studies have demonstrated unacceptable rates of virological failure with accumulation of INSTI mutations among the failures *(107,108).*

Overall, insufficient evidence supports using DTG in combination with TDF and 3TC as second-line ART for people for whom TDF + 3TC (or FTC) + EFV is failing as a first-line regimen. More data are needed on the efficacy of DTG among people with resistance to 3TC and TDF *(109).* Population-level surveys of HIV drug resistance are needed in countries transitioning to DTG to monitor emerging resistance to this drug.

Since 2019, more studies have become available examining the issue of transition to DTG-based regimens. The NADIA trial of second-line ART in seven sites in sub-Saharan Africa investigated whether second-line ART with DTG was non-inferior to once-daily RTV-boosted DRV (800 mg/100 mg) and whether TDF + 3TC was non-inferior to AZT + 3TC *(115)*. At baseline among 464 participants, 50% had the K65R drug resistance mutation and 87% had M184V. Of the participants, 58% had intermediate-high level resistance to TDF and 92% had resistance to 3TC. The 48-week viral load was <400 copies/mL for 90.2% in the DTG group and 91.7% in the DRV/r group, confirming the indicated non-inferiority of DTG. The proportion with confirmed viral rebound >1000 copies/mL was about 6% in each group, with no difference between groups (P = 0.90). Four participants with viral rebound in the DTG group had major DTG resistance mutations associated with intermediate or high-level resistance. The conclusions from the NADIA trial were that DTG with two NRTIs highly effectively suppresses viral loads to 48 weeks, even in a population in which many have extensive NRTI resistance and no predicted activity in prescribed NRTIs and that tenofovir can be maintained in second-line therapy without switching to AZT, with advantages for users and programmes.

Research gaps

Further evidence is needed to inform the routine use of TDF + 3TC + DTG in second-line regimens following the failure of TDF + 3TC (or FTC) + EFV, including more data on the efficacy of DTG among people with resistance to 3TC and TDF *(109)*.

Population-level surveys of HIV drug resistance are needed in countries transitioning to DTG to monitor emerging resistance to this drug.

Additional research is also required to better understand the choice and sequencing strategies in second- and third-line ART, especially for children and adolescents. Ongoing studies comparing the use of DTG and other INSTIs combined with other ARV drug classes will provide more data on appropriate second-line regimens, including NRTI-sparing and NRTI-limiting approaches.

Residual NRTI activity of TDF, 3TC and FTC, or reduced viral fitness, is likely in the presence of certain resistance mutations and could provide some protection against the selection of DTG resistance, but no clinical trials or observational studies have assessed their impact among people receiving the above-mentioned regimen.

4.6.3 Third-line ART

Background

WHO continues to monitor the available evidence on third-line ART. In 2010, WHO made recommendations on third-line ART in a context of limited evidence to guide treatment of people for whom second-line therapy is failing *(147)*. Although there were few studies with newer agents, cohort data showed high mortality among people for whom second-line ART had failed *(148)*. Salvage regimens were recommended with new drugs such as DRV/r, ETV and RAL with or without previously used ARV drugs that potentially maintained residual antiviral activity, especially from the NRTI class *(146,149,150)*. These recommendations were maintained in 2013 based on additional trial data *(151–154)*, but the need for more clinical and implementation research to guide the establishment of strategies and public health policies on third-line ART was emphasized *(155)*.

4.17 Recommendations (2013)

- **National programmes should develop policies for third-line ART** *(conditional recommendation, low-certainty evidence).*
- **Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and second-generation NNRTIs and PIs** *(conditional recommendation, low-certainty evidence).*
- **People receiving a failing second-line regimen with no new ARV drug options should continue with a tolerated regimen** *(conditional recommendation, very low-certainty evidence).*

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (155).*

Rationale and supporting evidence

Recent data from several randomized controlled trials and observational cohorts are available for DRV/r-, ETV-, DTG- and RAL-containing regimens for treatment-experienced adults; many of these ARV drugs were effective in prospective studies among children and adolescents, but most studies have been conducted in middle- to high-income settings *(156–164)*. Taken together, the data support the efficacy of new agents such as INSTIs, second-generation PIs and NNRTIs for people for whom the current second-line ART regimens have failed. However, multiple resistance to NRTI agents with reduced antiviral efficacy is common among ART-experienced people for whom first- and second-line regimens have already failed, and there is some uncertainty about whether maintaining or recycling previously used NRTIs provides clinical benefit, through viral fitness reduction and/or in vitro susceptibility enhancement caused by some mutations, combined with some residual antiviral activity of these drugs *(129,165)*. Further, since NRTI agents are often associated with cumulative toxicity, maintaining them in third-line ART may not be optimal and may involve increased pill burden and risk of drug–drug interactions. Avoiding NRTIs in third-line regimens is now more feasible because of the increasing availability of new ARV drug classes with different resistance profiles.

A systematic review and network meta-analysis was undertaken to determine whether NRTI-sparing new regimens (regimens that do not include NRTIs and that contain new drugs with a minimal risk of cross-resistance to previously used regimens) are comparable to NRTI-containing new regimens for the people for whom first- and second-line ART have failed. The pairwise meta-analysis showed that NRTI-sparing and NRTI-containing regimens were comparable in suppressing viral loads. For other outcomes, the data suggest that NRTI-sparing regimens may have better tolerability but that further evidence with highly treatment-experienced people is needed *(166)*.

More recently, the ACTG A5288 trial, a Phase 4, third-line ART study, found that regimens containing DRV/r + RAL were effective at achieving suppression of viral loads for those who demonstrated pre-existing LPV/r resistance in third-line ART. The study also showed how genotyping can help guide decisions to ensure that people receiving third-line ART can suppress viral loads *(167)*.

Table 4.9 Summary of sequencing options for first-line, second-line and third-line ART regimens and preferred and alternative first-line regimens for adults, adolescents and children

Populations	First-line regimen	Second-line regimen	Third-line regimen
Adults and adolescents	Two NRTIs + DTG	Two NRTIs + ATV/r (or LPV/r)	DRV/r[a] + 1–2 NRTIs ± DTG[b] Optimize the regimen using a genotype profile (if LPV is used in second-line ART)
		Two NRTIs + DRV/r	Optimize the regimen using a genotype profile
	Two NRTIs + EFV	Two NRTIs + DTG	Two NRTIs + (ATV/r, DRV/r or LPV/r) ± DTG[b]
Children	Two NRTIs + DTG	Two NRTIs + LPV/r (or ATV/r)	DRV/r[c] + 1–2 NRTIs ± DTG[d] Optimize the regimen using a genotype profile for children younger than three years
	Two NRTIs + LPV/r	Two NRTIs + DTG	DRV/r[c] + 1–2 NRTIs ± DTG[d] Optimize the regimen using a genotype profile for children younger than three years
	Two NRTIs + NNRTI	Two NRTIs + DTG	Two NRTIs + (ATV/r, LPV/r or DRV/r[c])± DTG[d]

[a] 600/100 mg twice daily

[b] 50 mg twice daily.

[c] DRV cannot be used for children younger than three years.

[d] For children older than 4 weeks and weighing at least 3 kg.

Implementation considerations

WHO estimates that less than 1% of the people taking ART globally are using third-line regimens, but the demand for third-line regimens will increase as access to viral load monitoring and use of first- and second-line ART continue to expand *(168)*. Third-line drugs generally cost more than first- and second-line regimens, which may limit the adoption of third-line regimens in many countries with limited resources. Although developing a policy on access to third-line ART is desirable, it should not compromise access to first- and second-line ART.

Consideration of sequencing options after first-line and second-line regimens fail

Among individuals for whom a NNRTI-based first-line regimen and DTG-based ART in second-line ART have failed, PI-based ART is an option to consider if they need third-line ART. In this case, the choice of PI (ATV/r, DRV/r or LPV/r) is based on cost, availability and convenience. Among individuals for whom a DTG-based first-line regimen and an ATV/r (or LPV/r) second-line regimen have failed, DRV/r (600 mg/100 mg twice daily) in combination with two NRTIs with the possible addition of DTG (50 mg twice daily) is a suitable option for third-line ART (see Table 4.8). If possible and feasible, countries can perform genotyping to identify optimal regimen selection for third-line ART, including the NRTI backbone.

Special considerations for children, adolescents and pregnant women

There have been few studies on the use of many newer ARV drugs as part of third-line regimens for children and adolescents and during pregnancy and breastfeeding; Pharmacokinetic and safety data are especially lacking. As a result, strategies that balance the benefits and risks need to be explored when second-line ART fails.

Given the limited data available, DRV and DTG are recommended for use in third-line regimens for children *(169)*. There is uncertainty about whether these drugs should be used in combination or as part of a standard NRTI-backbone regimen. DRV cannot be used for children younger than three years and is provided as a single drug only to selected countries through a donation programme *(169)*. RAL provides an alternative option for children for whom PI-based second-line ART has failed and should be considered when DTG cannot be used.

Children for whom a second-line regimen is failing with no new ARV drug options should continue with a tolerated regimen, similar to adults. If ART is stopped, attention should be paid to preventing opportunistic infections, relieving symptoms and managing pain.

There are limited data on using newer third-line drugs for women who are pregnant or breastfeeding.

Research gaps

Further research is needed to guide third-line ART strategies for resource-limited settings. Priorities include monitoring critical outcomes for people taking second-line ART, developing heat-stable formulations of DRV/r and evaluating the pharmacokinetics, safety and efficacy of new drugs not yet studied for children, adolescents and pregnant women.

4.7 Monitoring the response to ART

Recommendations for treatment monitoring (2013, 2016 and 2021)

Preferred monitoring approach

Viral load is recommended as the preferred monitoring approach to diagnose and confirm treatment failure[a] *(strong recommendation, low-certainty evidence).*

Point-of-care viral load testing may be used to monitor treatment among people living with HIV receiving ART[b] *(conditional recommendation, moderate-certainty evidence).*

Timing of treatment monitoring

Routine viral load monitoring can be carried out by six months, at 12 months and then every 12 months thereafter if the person is established on ART to synchronize with routine monitoring and evaluation reporting *(conditional recommendation, very-low-certainty evidence).*

See Fig. 4.2 for an updated treatment monitoring algorithm.

Role of CD4 cell count monitoring

In settings in which routine viral load monitoring is available, CD4 cell count[c] **monitoring can be stopped for individuals who are established on ART**[d] *(conditional recommendation, low-certainty evidence).*

In settings where viral load is not routinely available

If viral load testing is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure *(strong recommendation, moderate-certainty evidence).*

Use of dried blood spot specimens

Dried blood spot specimens using venous or capillary whole blood can be used to determine HIV viral load. A threshold of 1000 copies/mL can be used to determine virological failure when using dried blood spot samples, as defined for testing in plasma[a] *(conditional recommendation, low-certainty evidence).*

[a] Plasma specimens are preferred for viral load testing. Dried blood spot specimens are recommended in settings in which logistical, infrastructural or operational barriers prevent routine viral load monitoring using plasma specimens.

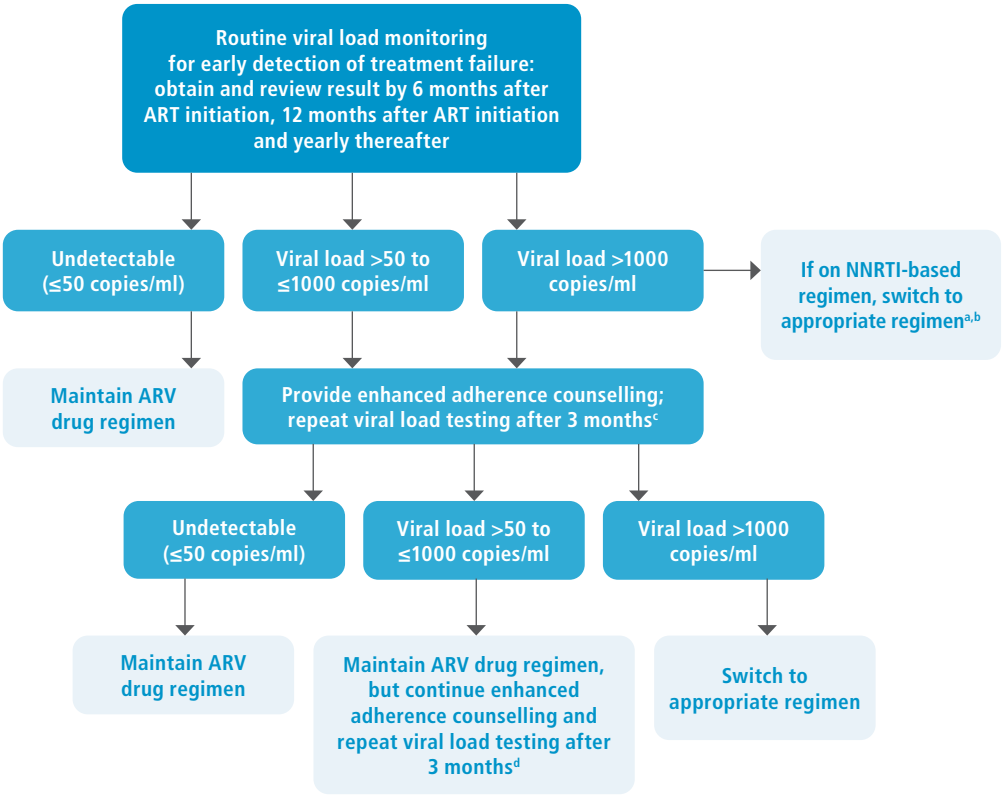
[b] See section 4.7.2 on using point-of-care viral load testing.

[c] The timing and use of CD4 remains the same as in the 2016 WHO consolidated guidelines *(3)*.

[d] Being established on ART includes suppressed viral loads (see section 7.3).

Sources: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (155)*; *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*; and *Guidelines: updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (62).*

Fig. 4.2 Treatment monitoring algorithm updated in 2021



Adherence counselling should be provided at all visits to ensure that viral suppression is maintained or given priority throughout care

[a] Switch after a single elevated viral load should be considered.

[b] A second viral load may be considered before regimen switch if DTG-based regimens are unavailable and the results of a viral load test can be returned and acted on rapidly.

[c] Conduct same-day testing using point-of-care viral load testing for a repeat viral load test, where available, to expedite the return of results. If not available, viral load specimens and results for a repeat viral load test should be given priority across the laboratory referral process (including specimen collection, testing and return of results). See subsection 4.7.2 on point-of-care viral load testing.

[d] Consider switching ART for those receiving NNRTI-based regimens based on clinical considerations and address any adherence concerns.

4.7.1 Monitoring after initiating ART

Clinical assessment and diagnostic tests play a key role in assessing individuals following a positive HIV diagnosis to assess for toxicity, coinfections, noncommunicable diseases and other comorbidities that may affect treatment response. Table 4.10 summarizes the recommended laboratory tests for screening and monitoring and approaches to screen for coinfections and noncommunicable diseases.

Table 4.10 Recommended tests for HIV screening and monitoring approaches for coinfections and noncommunicable diseases

Phase of HIV management	Recommended	Desirable
Receiving ART	HIV viral load test by six months and 12 months after initiating ART and every 12 months thereafter CD4 cell count every six months until established on ART	Serum creatinine and estimated glomerular filtration rate for TDF[a] Pregnancy test for women with childbearing potential not receiving family planning and receiving DTG or EFV 400 mg
Suspected treatment failure	Serum creatinine and estimated glomerular filtration rate for TDF[a] Pregnancy test for women with childbearing potential not receiving family planning and receiving DTG or EFV 400 mg	HBV (hepatitis B serum antigen) serology[b,c] (before switching ART regimen if this testing was not done or if the result was negative at baseline and the person was not vaccinated thereafter)

[a] Consider assessing for the presence of noncommunicable diseases that can influence ART management, such as hypertension and other cardiovascular diseases, diabetes and TB according to the WHO Package of Essential Noncommunicable Disease Interventions (PEN), Mental Health Gap Action Programme (mhGAP) or national standard protocols (see Chapter 6). Monitoring may include a range of tests, including serum creatinine and estimated glomerular filtration rate, serum phosphate and urine dipsticks for proteinuria and glycosuria.

[b] If feasible, hepatitis B serum antigen testing should be performed at baseline to identify people with HIV and HBV coinfection who should therefore initiate TDF-containing ART.

[c] For people coinfected with HIV and HBV who are already using TDF-containing regimens and develop ART failure, this NRTI should be maintained regardless of the selected second-line regimen.

4.7.2 Treatment monitoring of ART

Background

Monitoring people on ART is important to ensure successful treatment, identify adherence problems and determine whether ART regimens should be switched in case of treatment failure. Compared with clinical or immunological monitoring, viral load testing provides an early and more accurate indication of treatment failure and the need to switch from first-line to second-line drugs, reducing the accumulation of drug resistance mutations and improving clinical outcomes *(170)*. Measuring viral load also helps to discriminate between treatment failure and non-adherence, following enhanced adherence support. Further, viral load testing gives clients a measure of understanding, control and motivation to adhere to treatment and understand their HIV infection.

Table 4.11 WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens

Failure	Definition	Comments
Clinical failure	**Adults and adolescents** New or recurrent clinical event indicating severe immunodeficiency (WHO clinical stage 4 condition[a]) after six months of effective treatment **Children** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition except for TB) after six months of effective treatment	The condition must be differentiated from immune reconstitution inflammatory syndrome occurring after initiating ART For adults, certain WHO clinical stage 3 conditions (pulmonary TB and severe bacterial infections) may also indicate treatment failure[a]
Immunological failure	**Adults and adolescents** CD4 count at 250 cells/mm^3 following clinical failure[b] or Persistent CD4 cell count below 100 cells/mm^3	Without concomitant or recent infection to cause a transient decline in the CD4 cell count Current WHO clinical and immunological criteria have low sensitivity and positive predictive value for identifying individuals with virological failure. There is currently no proposed alternative definition of treatment failure and no validated alternative definition of immunological failure
Immunological failure	**Children** *Younger than five years* Persistent CD4 cell count below 200 cells/mm^3 *Older than five years* Persistent CD4 cell count below 100 cells/mm^3	
Virological failure	Viral load above 1000 copies/mL based on two consecutive viral load measurements three months apart, with adherence support following the first viral load test. ART switch after first viral load >1,000 copies/mL for those receiving NNRTI-based regimens	An individual must be taking ART for six months before it can be determined that a regimen has failed Individuals with viral load > 50 to < 1000 copies, maintain ARV regimen, enhance adherence counselling and repeat viral load testing after three months. Consider switch after second viral load > 50 to < 1000 copies/mL if people are on NNRTI-based ART

[a] See Chapter 5 and the list of clinical conditions associated with advanced or severe HIV disease associated with immunodeficiency in the 2016 WHO Consolidated HIV guidelines *(3)*.

[b] Previous guidelines defined immunological failure based on a fall from baseline, which is no longer applicable in the context of CD4-independent treatment initiation. The option of CD4 cell count at 250 cells/mm^3 following clinical failure is based on an analysis of data from Uganda and Zimbabwe *(171)*.

Viral load testing has been strongly recommended as the preferred approach to monitor treatment among people living with HIV since 2016. A treatment monitoring algorithm was developed to support the identification of people who need to switch to second-line ART if drug resistance is suspected *(3)*.

Since the 2016 viral load algorithm was developed, ART programmes in low- and middle-income countries have undergone changes that have altered the clinical ART context considerably. Two key programmatic shifts include rapid ART initiation (including on the same day as the diagnosis of HIV) and transition from first-line ART regimens containing NNRTIs, primarily EFV to DTG, an INSTI that has so far exhibited a very high barrier to drug resistance *(77,172)*. In addition, pretreatment drug resistance to NNRTI-based regimens has increased over the years *(85)*.

Four key considerations were reviewed to support algorithm changes:

- the timing of the first viral load test;
- the timing of the repeat viral load test after elevated viral load;
- immediately (based on a single viral load test) switching ART for those receiving NNRTI-based regimens; and
- treatment failure threshold.

Rationale and supporting evidence

Timing of the first viral load test

Earlier initial viral load testing was considered because of concerns about high levels of pretreatment NNRTI drug resistance among people initiating NNRTI-based ART. A first viral load test taken one or three months after initiating ART may support more rapid identification of poor adherence and/or potential pretreatment drug resistance that may negatively affect the response to treatment compared with the currently suggested first viral load test at six months after ART initiation. However, an earlier first viral load test could lead to unnecessary switching to second-line regimens.

In a pooled analysis *(173)* of non-pregnant adults including six studies *(174–179)* of people who had received ART for one month, 70% of those receiving DTG-based regimens had suppressed viral loads at <50 copies/mL versus only 20% of those receiving EFV-based regimens. After three months, 87% of those receiving DTG-based regimens and 63% of those receiving EFV-based regimens had suppressed viral loads. After six months, the regimens had few differences in overall suppression to <50 copies/mL. For children, data from randomized trials and observational studies suggest that infants and children may take longer than adults to have suppressed viral loads. For example, the ARROW trial showed that only 40% and 57% of children receiving LPV/r-based regimens were suppressed to <400 copies/mL at one and three months (respectively) after initiating ART with NNRTI-based therapy versus 94% by six months *(180)*. In the IMPAACT P1060 study, 81% of children achieved suppression to <50 copies/mL by six months if they started LPV/r-based ART but only 59% for NVP-based ART *(181)*.

Early suppression of viral loads was significantly decreased among people with baseline viral loads exceeding 100 000 copies/mL, with low rates of suppression of viral loads at month one even among people receiving DTG-based regimens *(173)*. Similarly, children with viral loads exceeding 100 000 copies/mL had poor suppression rates one and three months after initiating ART.

Detecting treatment failure resulting from pretreatment drug resistance earlier would be beneficial, especially for individuals starting NNRTI-based regimens. However, balancing this with potential overestimation of treatment failure if viral load is tested too early and results in subsequent unnecessary therapy switches is critical. The 2016 treatment monitoring algorithm suggests that the first viral load test be performed six months after initiating ART; however,

experience has shown that for many people living with HIV, sample collection, testing and result delivery occur beyond that time period. The updated treatment monitoring algorithm therefore encourages the first viral load result to be more urgently available and reviewed by six months after initiating ART.

Timing of repeat viral load test after an elevated viral load

The current viral load algorithm suggests a second viral load test 3–6 months after the initial elevated (>1000 copies/mL) viral load. A literature review found that the 3–6 months has been considered to lack clarity so that the timing of the repeat viral load test was inconsistently implemented and there are substantial delays in conducting repeat testing *(173)*. Multiple factors contributed to the prolonged time to repeat testing, including delayed specimen transport, delayed testing at the laboratory levels, issues with returning the results from the laboratory, barriers in returning the results at the facility level and patient factors that prevent them from returning for counselling and/or repeat viral load testing.

A defined and more precise time for the repeat viral load test may create more consistency and adherence and emphasize the importance of timely repeat viral load testing. Further, a repeat viral load test earlier than six months could minimize the further accumulation of drug resistance, especially for those receiving NNRTI-based regimens, and could minimize potential onward transmission. However, a viral load test one month after an elevated viral load result could overestimate treatment failure and cause unnecessary switches off treatment when people may require more time to achieve suppressed viral loads after adherence interventions. Performing the second viral load test earlier, three months after elevated viral load, may therefore support more rapid clinical action and prevent possible further selection of drug resistance and onward transmission of drug-resistant virus.

In addition, considering the use of point-of-care viral load testing for the repeat viral load test is encouraged to enable more rapid turnaround of test results and clinical action (see section 4.7.2).

Immediately (based on a single viral load test) switching ART for those receiving NNRTI-based regimens

A regimen switch after a single elevated viral load was only considered for NNRTI-based regimens and not for DTG- or PI-based regimens.

Resistance to NNRTIs among people for whom NNRTI-based ART has failed is high in low- and middle-income countries. The findings from nine national surveys of acquired drug resistance among adults measured after a single elevated viral load result showed that the prevalence of acquired drug resistance to NNRTIs ranged from 50% in Eswatini to 97% in Uganda at 12 months after initiating ART; the prevalence of acquired resistance to NNRTIs ranged from 71% in Nicaragua to 92% in Senegal 48 months or later after initiating ART *(85)*. Two studies reviewed drug resistance levels among adults living with HIV receiving TDF + 3TC or FTC + EFV regimens in several low- and middle-income countries *(182,183)*. In treatment cohorts from 1998 to 2015 of adults receiving regimens containing TDF, 3TC or FTC and EFV or NVP, the prevalence of NNRTI mutations at failure ranged from 42% in eastern Africa to 82% in western and central Africa *(182)*. Southern Africa had a mid-range of 59% NNRTI resistance *(183).* Further, children and adolescents receiving NNRTI-based regimens have high levels of drug resistance *(85).*

A systematic review and meta-analysis *(184)* found that 46% of the people receiving NNRTI-based first-line ART resuppressed at the next viral load test, indicating that many of those with

elevated viral loads may have had poor adherence. The proportion resuppressing was lower among children (31%) and adolescents (40%) than among adults (50%). Further, in several values and preferences surveys, both adolescents and adults living with HIV noted that they would prefer time to achieve suppression of viral loads *(62).*

Cost–effectiveness modelling suggests that switching adults from NNRTI-based ART to second-line ART after a single elevated viral load result (>1000 copies/mL) has health benefits and reduces HIV transmission and mortality, especially for those with drug resistance *(185,186).* Switching after a single elevated viral load is cost-effective based on a cost–effectiveness threshold of US$ 500 per DALY averted.

In summary, the available evidence suggests that 40–97% of the people in low- and middle-income countries receiving NNRTI-based ART regimens with a single elevated viral load have drug resistance and would benefit from immediately switching to second-line ART. Further, despite WHO recommendations, few people complete the viral load cascade (adherence counselling and repeat viral load testing) for those with a first elevated viral load result, with the available evidence suggesting that fewer than 25% receive a repeat viral load test *(187,188)*. Switching ART more quickly for those receiving NNRTI-based regimens would result in less risk of further selection of drug resistance and less risk of onward transmission, and this is critically important, especially for pregnant and breastfeeding women. Clinical support would be necessary to ensure more rapid switching to second-line ART.

Nevertheless, some people have a high viral load because of medication adherence challenges, and support should be provided to investigate and address these issues. Emphasizing adherence during ART initiation and throughout treatment is essential, including enhanced adherence counselling for those with an elevated viral load results. The Guideline Development Group determined that, although some people living with HIV receiving NNRTI-based regimens would not have drug resistance and may be unnecessarily switched to second-line ART, switching after a single elevated viral load result for those receiving NNRTI-based regimens would lead to significant personal and public health benefits. An immediate ART switch after a single elevated viral load result should not be considered for those receiving DTG- or PI-based regimens, since the likelihood of drug resistance is minimal according to current evidence.

Treatment failure threshold

A review identified 31 studies that examined low-level viraemia among adults receiving ART, of which 16 examined virological failure and/or disease progression, eight assessed drug resistance and seven evaluated HIV transmission *(189).* The studies reported a prevalence of low-level viraemia ranging from 3% to 26% (using various definitions). Low-level viraemia was generally defined as one or more viral load results for a single person of between 50 and 1000 copies/mL, with the studies including several viral load ranges less than 1000 copies/mL. The studies examined the relationship between low-level viraemia and future virological failure, which was defined as viral load >500 copies/mL or >1000 copies/mL after a period of low-level viraemia. Viral load ranges under 1000 copies/mL typically predicted future virological failure: a viral load between 50 and 200 copies/mL trended towards predicting future virological failure, and a viral load between 200 and 500 copies/mL statistically significantly predicted future virological failure.

Eight cohort studies examined the development of mutations associated with HIV drug resistance during episodes of low-level viraemia. All the studies included individuals with a history of NNRTI- and/or PI-based ARV drug regimens, and three studies also included

individuals receiving RAL, an INSTI. In all eight studies, detectable viral loads under 1000 copies/mL were associated with developing new drug resistance mutations when comparing initial drug resistance genotyping at baseline during suppression of viral loads and during or after episodes of low-level viraemia *(189).*

No studies assessed these outcomes for people receiving DTG, and whether low-level viraemia is a clinically relevant phenomenon for people receiving DTG- or PI-based regimens remains unclear.

HIV transmission

The review included seven studies on HIV transmission during documented episodes of low-level viraemia, comprising five cohort studies and two randomized controlled trials *(189).* Three studies showed no evidence of HIV transmission within adult couples when the HIV-positive partner had viral loads under 200 copies/mL, and another study showed no transmission events when the viral load was under 1500 copies/mL. Low-level viraemia (<1000 copies/mL) was not associated with sexual transmission.

A review undertaken to update the Spectrum mathematical model *(190)* summarized the risk of vertical transmission according to maternal viral load. The subset of studies comparing transmission with viral load below and above 1000 copies/mL showed overall 0.22% versus 5.8% transmission rates, respectively (0.22% versus 5.8% for formula feeding and 0.38 versus 5.3% for breastfeeding). The subset of studies comparing viral load below and above 400 copies/mL showed overall 0.41% versus 3.3% transmission rates, respectively (0.36% versus 3.5% for formula feeding and 1.8% versus 7.3% for breastfeeding). Although the time of transmission is difficult to determine, mother-to-child transmission was observed, albeit at low proportions, even with low levels of virus.

No studies were identified evaluating the transmissibility of HIV by sharing injecting drug use equipment when a person's viral load is under the current 1000 copies/mL threshold.

Implementation considerations for the treatment monitoring algorithm

Many settings rely on dried blood spot, point-of-care technologies or other alternative specimen type or technology to support expanded access to viral load testing. The diagnostic accuracy, sensitivity and specificity of dried blood spots and point-of-care viral load technologies to detect treatment failure at theoretically lower treatment failure thresholds varies (Table 4.1) *(191,192).* Several technologies could reliably perform at lower treatment failure thresholds; however, others had considerably poorer performance. Most technologies were unable to achieve sensitivity and/or specificity greater than 90% when the treatment failure threshold of undetectable versus detectable was used. For some, the confidence intervals are wide, and additional studies are necessary to better understand potential performance.

Experts noted the value of distinguishing suppression of viral loads or undetectable virus from treatment failure that requires switching therapy. Further, the significant transition efforts towards DTG-based regimens across countries should be recognized. The Guideline Development Group determined that the treatment failure threshold should remain at 1000 copies/mL. Viral suppression and undetectability, however, are defined as viral load equal to or less than 50 copies/mL

Table 4.12 Diagnostic accuracy (%) of alternative sample collection types (dried blood spot) or point of care with lower theoretical treatment failure thresholds

Sensitivity (copies/mL)	Abbott 1-spot[a]	Abbott 2-spot[a]	Biocentric	bioMerieux[b]	Hologic[c]	Roche FVE[d]	Roche SPEX[d]	Siemens	Cepheid
1000	88 (50–98)	93 (84–97)	95 (71–99)	83 (78–87)	85 (44–98)	95 (85–98)	98 (96–99)	91 (69–98)	96 (95–97)
800	92 (5–100)	93 (83–97)	99 (44–100)	85 (80–89)	93 (31–100)	95 (87–98)	99 (96–100)	91 (75–97)	97 (96–98)
600	93 (0–100)	93 (84–97)	99 (60–100)	89 (84–92)	95 (28–100)	94 (84–98)	99 (96–100)	93 (84–97)	97 (96–98)
500	93 (0–100)	93 (84–97)	98 (67–100)	89 (85–92)	95 (29–100)	93 (82–98)	99 (96–100)	97 (66–100)	97 (96–98)
400	94 (0–100)	92 (84–97)	98 (60–100)	90 (86–93)	95 (28–100)	92 (81–97)	99 (95–100)	97 (63–100)	96 (95–97)
200	97 (0–100)	91 (83–95)	98 (65–100)	89 (84–93)	95 (22–100)	89 (76–96)	99 (95–100)	98 (72–100)	95 (93–97)
Detectable	93 (63–99)	93 (76–98)	98 (60–100)	88 (75–95)	75 (52–90)	97 (58–100)	99 (95–100)	90 (84–94)	93 (88–96)

Sensitivity (copies/mL)	Abbott 1-spot[a]	Abbott 2-spot[a]	Biocentric	bioMerieux[b]	Hologic[c]	Roche FVE[d]	Roche SPEX[d]	Siemens	Cepheid
1000	99 (68–100)	91 (82–96)	55 (35–74)	95 (89–98)	73 (31–94)	94 (72–99)	48 (23–75)	88 (75–94)	97 (93–98)
800	99 (24–100)	92 (83–96)	38 (11–76)	96 (91–98)	72 (42–90)	93 (65–99)	38 (13–70)	87 (68–95)	97 (93–99)
600	99 (12–100)	93 (81–97)	28 (6–71)	95 (91–97)	89 (50–99)	93 (68–99)	33 (12–65)	79 (61–90)	96 (92–98)
500	99 (9–100)	93 (82–98)	24 (4–68)	95 (91–98)	89 (50–98)	92 (68–98)	30 (10–62)	66 (31–89)	95 (90–98)
400	99 (8–100)	93 (80–98)	11 (1–73)	96 (91–98)	88 (48–98)	92 (68–98)	28 (9–60)	65 (25–91)	96 (93–98)
200	99 (5–100)	97 (92–99)	15 (1–70)	93 (89–95)	81 (72–89)	92 (71–98)	25 (8–58)	65 (26–90)	98 (95–99)
Detectable	93 (66–99)	79 (8–99)	19 (5–51)	93 (90–96)	87 (67–96)	58 (6–97)	4 (0–54)	69 (41–88)	81 (65–90)

[a] Abbott RealTime HIV-1.
[b] bioMerieux NucliSENS® EasyQ® HIV-1 v2.0
[c] Hologic Aptima HIV-1 Quant Dx Assay.
[d] Roche COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, version 2.0

The blue shaded cells represent those with <85% sensitivity or specificity.
Sources: Sacks et al. *(41)* and Vojnov et al. *(71,72)*.

Emphasizing and strengthening adherence counselling during ART initiation and throughout treatment is essential, including and especially after elevated viral load results. Viral load results can be a motivation for adherence and achieving suppression of viral loads. Consideration should be made to ensure adequate training on ART for clinicians, health-care providers and lay and peer providers, including transition to optimal regimens, treatment failure, switching therapy and adherence support.

For some populations, obtaining more rapid results by using same-day point-of-care testing may be especially beneficial (Box 4.5). Testing pregnant and breastfeeding women with point-of-care technologies will enable more rapid clinical decision-making to prevent transmission. Drug resistance rates are typically higher among infants, children and adolescents than among adults, and rapid results may thus prevent the selection of drug resistance mutations and preserve future treatment options while preventing the selection of drug resistance in the remaining high-risk populations.

Box 4.4 shows specific implementation considerations for monitoring the treatment of pregnant and breastfeeding women.

A treatment failure threshold must not be considered synonymous with being undetectable or suppressed. All people living with HIV should be supported with adherence counselling to achieve suppression of viral loads (undetectable); however, treatment failure should be considered for those with a repeat viral load result >1000 copies/mL three months after a first viral load result >1000 copies/mL. Those with low-level viraemia (50–1000 copies/mL) need to be provided with enhanced adherence counselling and additional viral load testing to promote suppression of viral loads.

Box 4.4. Implementation considerations for monitoring treatment of pregnant and breastfeeding women

- **Whenever possible, use same-day point-of-care testing for viral load testing of pregnant and breastfeeding women** to expedite the return of results and clinical decision-making. If this is not available, viral load specimens and results for pregnant and breastfeeding women should be given priority across the laboratory referral process (including specimen collection, testing and return of results).
- **Adherence counselling** should be provided at all antenatal care and postnatal visits to ensure that viral suppression is maintained throughout pregnancy and breastfeeding.
- **For all pregnant women, regardless of ART initiation timing:** conduct viral load testing at 34–36 weeks of gestation (or at the latest at delivery) to identify women who may be at risk of treatment failure and/or may deliver infants at higher risk of perinatal transmission.

  Action: if viral load >1000 copies/ml, follow the treatment monitoring algorithm[a] and provide enhanced postnatal prophylaxis[b] for the infant. Where available, consider infant nucleic acid testing at birth.[b]

In addition:

a) **For pregnant women receiving ART before conception:** conduct a viral load test at the first antenatal care visit (or when first presenting) to identify women at increased risk of in utero transmission.

   Action: If viral load >1000 copies/ml, follow treatment monitoring algorithm[a] and consider infant nucleic acid testing at birth,[b] where available.

b) **For pregnant women starting ART during pregnancy:** conduct a viral load by three months after ART initiation to ensure that there has been rapid viral suppression.[c]

   Action: If viral load >1000 copies/ml,[a] follow the treatment monitoring algorithm.[a] Regardless of the maternal viral load, the infants of mothers starting ART at any time during pregnancy could be considered for birth testing,[b] where available.

- **For all breastfeeding women, regardless of when ART was initiated:** conduct a viral load test three months after delivery and every six months thereafter to detect viraemic episodes during the postnatal period.

  Action: if viral load >1000 copies/ml,[a] follow the treatment monitoring algorithm,[a] conduct infant HIV testing immediately[d] and consider reinitiating enhanced postnatal prophylaxis for the infant.[b,e]

[a] See Fig. 4.2.

[b] See the programmatic update on HIV diagnosis and ARV drug use for HIV-exposed infants *(193).*

[c] If viral load testing is expected to be undertaken in close proximity to the planned viral load at 34–36 weeks of gestation (see above), the first viral load test can be delayed until weeks 34–36 of gestation.

[d] Conduct same-day testing using point-of-care infant diagnosis, where available, to expedite the return of results. See Chapter 2 for details on point-of care infant diagnosis.

[e] Consider reinitiating and continuing enhanced postnatal prophylaxis until the results are returned or same-day testing is negative. Begin ART if the infant is diagnosed with HIV (193).

Research gaps

Areas that would benefit from further research include how low-level viraemia relates to the development of drug resistance mutations to DTG and other optimized ARV drugs and whether low-level viraemia is clinically relevant for people living with HIV receiving DTG-based regimens. Considering the very low levels of drug resistance, the role of drug resistance testing is unclear in a treatment failure algorithm for people living with HIV receiving DTG-based treatment to minimize unnecessary switches from this regimen. Additional data for children and adolescents would support optimized treatment monitoring in these populations for which drug resistance is a critical issue. Finally, there is limited evidence to determine the ideal treatment monitoring algorithm for pregnant and breastfeeding women receiving ART.

4.7.3 Point-of-care viral load testing

Recommendation (2021)

Point-of-care viral load testing may be used to monitor treatment among people living with HIV receiving ART *(conditional recommendation, moderate-certainty evidence).*

Source: *Guidelines: updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring (62).*

Background

In 2016, viral load testing was strongly recommended as the preferred approach to monitor treatment among people living with HIV, with the associated development of a treatment monitoring algorithm to identify potential adherence challenges or drug resistance – with the latter requiring people to switch to a second-line ART regimen *(3)*. There has been significant uptake of viral load testing since 2016, with more than 20 million viral load tests being performed across low- and middle-income countries in 2019 *(194)*. Scaling up laboratory capacity and sample collection networks has facilitated increased access to diagnostics, in general and specifically for HIV viral load; however, challenges remain, with inadequate access, infrastructural barriers, human resource shortages, long turnaround times and clinical utilization of test results.

In recent years, several new technologies have emerged on the market that enable much more simplified, easy-to-use point-of-care testing, including for viral load testing. These technologies require separating plasma from a whole-blood specimen, derived from either venepuncture or finger- or heel-prick specimens, and return results within 1–2 hours. Two of these technologies have undergone WHO prequalification assessment and are listed for procurement by Member States *(195)*.

The addition of point-of-care viral load testing is a progressive step towards improving the use of viral load in a variety of settings and may also be considered for use in specific populations needing more rapid test results, including people with advanced HIV disease, infants, children, adolescents, people for whom treatment is suspected of failing and pregnant and breastfeeding women.

Rationale and supporting evidence

Summary of review findings

A systematic review identified three studies (one randomized controlled trial – the STREAM study – and two observational studies) comparing point-of-care testing directly with the standard of care *(196–199)*. The overall certainty of the evidence in this review was rated as moderate (high quality for the randomized controlled trial and moderate for the observational studies). There were some risks of potential bias from missing data and related to sampling in the observational studies.

Return of test results

In the STREAM study, using point-of-care testing, same-day results were available for clinicians 99% of the time (median time to return result: 0 days); and for patients, 99% of the time (median: 0 days) *(197)*. For the standard of care, same-day results were available for clinicians <25% of the time (median: 2 days); and for patients, <1% of the time (median: 28 days). The observational studies also demonstrated substantially shorter time to return results for both clinicians and patients using point-of-care testing compared with the standard of care. The hazard ratio comparing point-of-care to standard-of-care testing for returning results to clinicians was 11.7 (95% CI 8.9–15.3) and was 17.7 (95% CI 13.0–24.12) for returning the results to patients. In the randomized controlled trial, >99% of patients received their results with point-of-care testing; however, only 82% of patients ever received their results with standard-of-care testing, an absolute risk difference of 18% (95% CI 14–22%). Overall, the evidence had moderate to high certainty.

Clinical action following elevated viral load result

In the STREAM study, 100% of the people identified with unsuppressed viral loads initiated second-line ART following point-of-care testing (at a median of 0 days) versus 44% (median of 76 days) following standard-of-care testing [hazard ratio 10.9 (95% CI 2.1–57.5)] *(197)*. The estimated time to any clinical action (either enhanced adherence counselling or switching to a second-line regimen) was also shorter following point-of-care testing versus standard-of-care testing in observational studies. The evidence was of moderate certainty overall.

Long-term suppression of viral loads and retention in care

Only the randomized controlled trial included long-term suppression of viral loads and/or retention in care outcomes *(197)*. Of everyone who received a point-of-care test, 90% were retained in care and achieved suppression of viral loads (<200 copies/mL) after 12 months of follow-up versus 76% of those who received a standard-of-care test (risk difference 14% [95% CI 6–21%]). The evidence was of moderate certainty overall.

Transfer to differentiated care for people with sustained suppression of viral loads

Only the randomized controlled trial included the transfer to differentiated care outcome for people with sustained suppression of viral loads *(197)*. Of the people in the point-of-care arm, 60% (versus 27% in the standard-of-care arm) had initiated differentiated care 18 months after initiating ART, an absolute difference of 33% (95% CI 23–42%). The time from ART initiation to transfer for differentiated care was also shorter following point-of-care testing (median 168 days) than standard-of-care testing (median 261 days), hazard ratio 3.5 (95% CI 2.5–4.8). The evidence was of high certainty overall.

Potential high-risk groups: children, adolescents, pregnant and breastfeeding women and people for whom treatment failure is suspected

No studies assessed the need and/or importance of ensuring same-day test results for high-risk groups.

Costs and cost–effectiveness

Three studies evaluated the cost–effectiveness of point-of-care viral load testing compared with laboratory-based testing; two were conducted in Kenya and one in South Africa *(200–202)*. Overall, point-of-care testing across the three studies was found to be cost-effective compared with the standard of care even when accounting for local context and different implementation approaches. These studies did not include potential cost savings to patients associated with fewer facility visits.

Values and preferences

WHO carried out a survey among people living with HIV to understand their values and preferences for point-of-care viral load testing versus laboratory-based testing *(62)*. The majority (81%) of the 43 respondents stated that monitoring their treatment using same-day testing would be acceptable, and 63% prefer point-of-care viral load testing to laboratory-based testing. The primary reason (77%) for getting a point-of-care viral load test was to know immediately whether treatment was working well, and changing treatment without coming back was second (21%).

In addition, an online survey *(62)* was provided to 51 health-care workers and 43 programme managers to determine how they perceive the acceptability and feasibility of point-of-care viral load testing. The majority (91%) of health-care workers stated that point-of-care testing would be acceptable or somewhat acceptable. Fifty-three per cent preferred point-of-care viral load testing over laboratory-based testing; 73% thought nurses and other health-care workers would be able to perform the point-of-care viral load testing. The majority (63%) of health-care workers thought that the workload would increase when point-of-care viral load testing is introduced. The majority of programme managers (58%) surveyed already have a policy for point-of-care viral load testing; however, 98% indicated that most viral load tests were performed using standard-of-care laboratory-based testing. Point-of-care viral load testing was thought to be more acceptable (53%) than laboratory-based testing (13% were neutral). Among the respondents, 26% preferred point-of-care viral load testing, and 43% thought that having both point-of-care and laboratory-based viral load testing would be best. Programme managers thought that the workload would increase if point-of-care viral load testing was implemented either in the laboratory (53%) or in the clinic (62%). The majority (68%) thought that nurses would feel comfortable doing point-of-care viral load testing.

Diagnostic accuracy

A systematic review included an individual patient data meta-analysis for the Cepheid GeneXpert®, using 14 data sets from 13 eligible studies *(191).* The pooled sensitivity was 96.5% (95% CI: 95.1–97.5%) and pooled specificity was 96.6% (95% CI: 92.9–98.4%) for a treatment failure threshold of 1000 copies/mL. The mean bias was 0.04 log copies/mL.

Two studies have provided accuracy data on the Abbott m-PIMA™ device *(34,42,203,204).* A study from Kenya reported a sensitivity of 95.4% (95% CI: 89.7–98.5%) and specificity of 96.0% (95% CI: 93.7–97.6%) for a treatment failure threshold of 1000 copies/mL *(35)*. The mean bias was 0.16 log copies/mL. A second study from Brazil had a sensitivity of 97.1% (95% CI: 94.2–98.8%) and specificity of 76.9% (95% CI: 69.8–83.1%) for a treatment failure threshold of 1000 copies/mL *(204)*.

Feasibility

Technologies are on the market and available for use at the point of care. Two already have WHO prequalification *(195)*; many such devices have already been procured and are in use for TB testing (Cepheid GeneXpert®) or viral load already (Abbott m-Pima™ and/or Cepheid GeneXpert®). The currently available technologies both require plasma separation from whole blood and therefore additional third-party equipment and expertise. The Abbott m-PIMA™ device can run about 6–8 tests per day, and the Cepheid GeneXpert® device can perform about 6–8 tests per module per day. Across 140 high-burden developing countries (Cepheid's High Burden Developing Country programme *(205)*), more than 11 694 devices have been delivered, comprising 52 058 modules. Nearly 12 million GeneXpert® TB cartridges were procured per year in 2017 and 2018; however, one analysis suggests that only 1.2 tests per module per day are currently being run *(205)*. This leaves available capacity for expanding TB testing and considering HIV infant and viral load testing. Nevertheless, performing point-of-care viral load testing for all people living with HIV receiving ART may require significantly more volumes than the testing capacity at most health-care facilities; robust and deliberate mapping and network optimization as well as setting priorities for who is tested should therefore be considered.

Equity

Ethical and equity considerations were summarized to guide the discussions during the guideline meeting *(206)*. Given the likely benefits associated with point-of-care testing for viral load, all efforts should be undertaken to make this part of routine clinical care. Doing so would be in keeping with both equity and social justice considerations by recourse to similar arguments, as in the context of point-of-care testing for infant diagnosis. The goals of social justice are the fair distribution of benefits and burdens at the population level, including treating people as equally important (which includes, specifically, equity considerations).

Providing point-of-care viral load testing would promote treating those with HIV as equally important to those without HIV for the purposes of maintaining good health. Moreover, access to health care would also seem to entail access to the best standards of care possible.

From an ethics viewpoint, it does matter that point-of-care viral load testing might conflict with the use of existing resources for other disease areas. How to resolve this dilemma would likely not be unanimous among bioethicists. The first way of resolving this challenge would appeal to an understanding of social justice that often requires distributing scarce resources based on greatest need. Conversely, one might argue based on utility (maximization of resources) that scarce resources, such as GeneXpert®, should be used to obtain the greatest overall benefit in a community, regardless of disease area. Solidarity would encourage that the global community come together to provide the greater resources necessary to perform all the point-of-care testing if that is what is best for the community. Efforts should be taken to work with global organizations to procure the necessary technology before engaging in the ethical trade-offs between considerations of social justice and utility.

Rationale

The Guideline Development Group formulated a conditional recommendation favouring point-of-care viral load testing to monitor the treatment of people living with HIV receiving ART. This was based on moderate-certainty evidence and their judgement that the benefits of introducing point-of-care viral load testing for monitoring treatment outweigh the harm. In summary, the following benefits include, but are not limited to:

- more rapid testing and return of results to clinicians and people living with HIV;
- fewer health-care facility visits for people living with HIV to receive results and more

reliability on the timing of results and possibly more likelihood for test recording;

- increased likelihood of clinical action following elevated viral load;
- increased likelihood of long-term suppression of viral loads, retention in care and transfer to differentiated care for those with sustained suppression of viral loads; and
- improved quality of care and services.

No major notable harm was identified; however, some concerns were noted around the generally higher costs of testing. In addition, it was acknowledged that the tests currently available and on the market have limited test throughput: depending on daily volumes, health-care facilities may have to triage those who should receive a point-of-care test and those who should be referred for standard-of-care testing.

The Guideline Development Group made a conditional recommendation for all people living with HIV, based on variability and uncertainty around the resource requirements and the feasibility and appropriateness of implementation in different settings. Important implementation considerations were developed to help to guide countries moving forward and are summarized in the following section.

Implementation considerations for point-of-care viral load

Several implementation considerations were highlighted.

First, point-of-care viral load technologies should be considered and used within the current treatment monitoring algorithm (Fig. 4.1).

Second, access to high-quality diagnostic testing should be continually expanded across HIV and other molecular testing needs, ideally combining laboratory-based and point-of- care technologies in an integrated laboratory network. Additional procurement and optimal placement of point-of-care technologies should be considered within the context of the overall health system, including other disease programmes and needs. This will create efficiency and support expansion and improved diagnostic services for HIV and other diseases (TB, HIV viral load, etc.). In addition, strengthening integrated diagnostic systems may be considered to improve service and maintenance, specimen transport, training, quality assurance, mentorship and supervision, data systems, etc.

However, conducting point-of-care viral load testing for all people living with HIV receiving ART may require significantly more volume than the testing capacity at most health-care facilities; robust and deliberate mapping and network optimization as well as setting priorities among people living with HIV should therefore be considered (Box 4.5). Testing pregnant and breastfeeding women with point-of-care technologies will enable more rapid clinical decision-making to prevent vertical transmission. Drug resistance rates are typically higher among infants, children and adolescents than among adults, and rapid results may thus prevent the selection of drug resistance mutations and preserve future treatment options, while preventing selection of drug resistance in the remaining high-risk populations is critical.

Box 4.5. Priorities for point-of-care viral load testing

The following populations should be given priority for point-of-care viral load testing:

- Pregnant and breastfeeding women
- Infants, children and adolescents
- People requiring a repeat viral load after a first elevated viral load
- People for whom treatment failure is suspected
- People presenting sick, living with advanced HIV disease or having a known opportunistic infection (TB, cryptococcal infection, etc.)
- First scheduled viral load test for people re-entering care

Finally, priority should be given to ensuring adequate human resources, training (including technical, result interpretation, counselling and supply chain), service and maintenance and quality assurance. Further, using the results is key to optimizing the use of viral load testing. Clear messaging, communication and literacy considerations should be implemented to support scale-up, trust and use, in close collaboration with community groups. Strengthening treatment literacy and the importance of viral load testing within treatment monitoring for people living with HIV will be essential to support the management of people's health. Maximizing the clinical impact of point-of-care testing and reducing delays in switching treatment requires ongoing strengthening of treatment and care services for all people living with HIV, including adherence interventions and retention.

Research gaps

Further research could evaluate how to optimize the implementation of point-of-care technologies across a variety of settings. Additional clinical research on retention in care, morbidity and mortality for point-of-care viral load testing versus laboratory-based testing would be useful. Implementation research could evaluate quality assurance approaches for sustainable delivery of point-of-care viral load testing. Further research could support the clinical impact of setting priorities among people living with HIV for point-of-care testing, when triage is required; implementation research could seek to understand the practical considerations of how to do this.

Understanding the benefits and harm of using semiquantitative approaches for determining viral load would be helpful. Additional research on cost–effectiveness, staff time, patients' perspectives and clinical use of results for both laboratory-based and point-of-care viral load testing would be beneficial as would solutions to improve this. Finally, investigating the potential for a dual-claim point-of-care test that can be used across infants, children and adults, both for HIV diagnosis and viral load, could streamline the supply chain and create more efficient diagnostic systems.

4.7.4 Other clinical and diagnostic considerations

Determining treatment failure in the absence of viral load monitoring

If viral load monitoring is not available, clinical monitoring and CD4 cell count monitoring could be considered. However, immunological and clinical criteria have poor sensitivity and specificity to detect treatment failure, especially at higher CD4 cell counts, and more accurate immunological criteria have not yet been identified *(207)*. In the absence of better criteria to predict treatment failure, using CD4 cell count and clinical assessment is important to identify those at the highest risk of disease progression and mortality. Countries should continue to scale up viral load testing as the preferred treatment monitoring approach.

Stopping CD4 monitoring where viral load testing is available

A systematic review identified 13 studies carried out in Asia, Africa, Europe, the United States of America and Australia and found that CD4 cell count declines among adults and children who have suppressed viral loads on ART are rare and mainly transient events that are mostly explained by non-HIV factors, such as concomitant immunosuppressive therapy. Overall, the evidence suggests that, for individuals established on ART who are monitored virologically, routine CD4 cell count monitoring adds little value and could be stopped. This recommendation is further supported by the substantial cost savings that could be gained from stopping routine CD4 cell count monitoring *(208–210)*.

Alternative specimen types for viral load testing when traditional plasma cannot be widely used

Although plasma specimens are the standard for viral load testing, their use is restricted by the limited ambient temperature stability of viral biomarkers in whole blood and plasma during storage and transport and the limited cold-chain availability between many health-care facilities in resource-limited settings. Many options are available to countries to support the scaling up of viral load testing, and suppliers include should these alternative options within their intended use claims and seek regulatory approval and WHO prequalification to support country scale-up and access to viral load testing.

Dried blood spot specimens

Dried blood spot specimens for HIV testing have been routinely used for collecting and shipping infant HIV diagnosis specimens for testing by PCR in centralized laboratories. They are beneficial since they do not require centrifuges, refrigerators or freezers at the specimen collection site, can be stored and transported for weeks at ambient temperature and require a simple finger-prick or heel-stick blood specimen that can be prepared by lower cadres of health-care facility staff. Similar benefits could be achieved by using dried blood spot specimens for viral load testing programmes in resource-limited settings.

Dried blood spot specimens for viral load testing using nucleic acid–based detection methods use whole blood as the input specimen, which can result in extraction and detection of proviral DNA and intracellular RNA in addition to the primary biomarker target of free viral RNA circulating in the plasma. Together, this may result in over-quantification of the viral load result.

A systematic review identified 43 studies that compared dried blood spot specimens to plasma specimens for viral load testing. Overall, the performance of dried blood spot specimens had acceptable sensitivity for identifying virological failure (>85%) and specificity (>80%) compared with a reference standard of the same assay testing using a matched plasma specimen at 1000 copies/mL for most commonly used technologies (see Table 4.11) *(211).* Although this reduced sensitivity means that plasma specimens are preferred for viral load testing, modelling suggests that if viral load testing with dried blood spot specimens can be performed with reasonable sensitivity and specificity (>85%), then the costs and outcomes are similar *(212)*.

Dried blood spot specimens provide a way to improve the coverage and reach of viral load testing where the preparation and transport of plasma specimens may be limited by cold-chain requirements or transport challenges. However, limited progress has been made in ensuring the quality of using dried blood spot specimens for HIV viral load testing through international regulatory approval.

Dried plasma spot specimens

Dried plasma spot specimens for HIV testing are an alternative specimen type developed similarly to the well-established dried blood spot specimens that have been routinely used for collecting and shipping infant HIV diagnosis specimens for testing by PCR in centralized laboratories. These specimens use the same or similar filter paper as dried blood spot specimens for viral load or infant diagnosis, using plasma instead of whole blood. Although they require centrifugation or collection of plasma for spotting on the card, they can be stored and transported for weeks at ambient temperature. An advantage of dried plasma spot specimens is that plasma separation and use remove the detection and quantification of intracellular RNA and proviral DNA often observed with whole-blood specimens; however, the smaller input specimen volume may limit the perfect comparability with liquid plasma specimens.

The results from 17 independent technical evaluations across 12 countries and looking at four commercially available technologies were included in a comprehensive meta-analysis that included almost 2000 paired dried plasma spot–plasma data points *(213)*. The performance of dried plasma spot specimens across all technologies was comparable to using traditional liquid plasma. As expected, since the input specimen type, plasma, was used, limited upward and downward misclassification was observed. However, information focusing on the feasibility and operational best practices of using dried plasma spot specimens within viral load scale-up plans has been limited.

Plasma separation cards and simple devices can support the expansion of viral load testing using plasma specimens. It is essential that suppliers include these alternative options within their intended use claims and seek regulatory approval and WHO prequalification to support country scale-up and access to viral load testing.

Implementation considerations for treatment monitoring

In settings where viral load monitoring is widely available, consideration could be given to more frequent viral load testing for children and adolescents who are at the highest risk viral failure and for whom monitoring of adherence might be particularly challenging *(3)*.

Diagnostic tests are not of significant value unless the test results are used clinically. To create effective health services that provide optimal care and treatment to people living with HIV, programmes must revitalize and invest in the laboratory–clinical interface and ensure that the right training, tools and environment are available to improve the uptake and use of all diagnostic results in a timely manner *(3)*. In addition, improving and ensuring adherence counselling is critical to supporting optimal patient care (see section 7.4).

Further, ensuring that health-care providers are adequately trained to conduct timely viral load testing and take appropriate clinical actions when the viral load is high, such as intensified adherence support and possible regimen switches, will be critical *(3)*.

Views expressed during a community consultation undertaken for these guidelines underscored the importance of improving literacy about viral load. It is generally understood that access to viral load gives clients a measure of understanding, control and motivation to adhere to and manage their HIV *(3)*.

CD4 cell count testing still has an important role to play since it remains the best predictor for disease status and immediate risk of death and thus should be used to identify those who have advanced HIV disease. Everyone entering or re-entering care should receive a CD4 cell count test at treatment baseline and as clinically indicated for people who are clinically unstable or have advanced HIV disease.

4.7.5 Monitoring ARV drug resistance

Current approaches to genotype testing remain too costly and complex for routine use as part of a public health approach, and WHO does not currently recommend routine genotype testing to guide ART regimen selection apart from optimizing third-line regimen for people pre-exposed to the anchor drugs: the third agent in addition to the double NRTI backbone.

An increasing number of low- and middle-income countries are starting to use drug resistance genotyping to inform treatment decisions. Based on the 2021 Global AIDS Monitoring survey, about 65% of 55 low- and middle-income countries reported using resistance testing for individual management. Genotyping tests can be used to minimize unnecessary treatment switches from first-line to second-line ART and from second- to third-line ART, by determining predicted susceptibility to the anchor drugs used in first- and second-line ART, respectively. In addition, genotyping testing can inform optimal third-line ARV drug composition. WHO recognizes the value of genotyping for individual management in such situations provided that the coverage of viral load test is high, resources are available, laboratory capacity is in place and in-country expertise exists to properly interpret genotyping results.

To inform national policies on ART, WHO recommends population-level periodic surveillance of HIV drug resistance through nationally representative surveys. Surveillance should target populations initiating ART, populations receiving ART, treatment-naive children younger than or equal to 18 months newly diagnosed with HIV and PrEP users who acquire HIV (see Chapter 8) *(214–218)*. The results of these surveys support the choice of recommended first- and second-line ART and pre- and post-exposure prophylaxis.

Many factors are associated with the emergence of HIV drug resistance. Broadly these factors may be divided into three categories: (1) viral factors (such as HIV subtype, replication capacity and pre-existing polymorphisms); (2) drug-related factors (such as drug potency, pharmacokinetics, drug–drug interactions, tolerance and genetic barriers to resistance); and (3) programme factors (such as adherence to prescribed ART, drug supply continuity and retention on treatment). Although viral and drug-related factors are often beyond the control of public health authorities or programme managers, monitoring ART programme factors can alert ART clinics and national programme planners to situations that may favour population-level virological failure and/or the emergence of resistance. Once such situations have been identified, clinic- or programme-level action may be implemented to optimize care, thus minimizing the emergence of preventable HIV drug resistance.

In addition, WHO recommends that HIV drug resistance prevention activities be integrated into national HIV programmes through the annual monitoring of seven quality-of-care indicators, also known as early warning indicators (see Chapter 8):

- total attrition from ART;
- people living with HIV who have suppressed viral loads;
- viral load testing coverage;
- appropriate second viral load test;
- ARV medicine stock-outs;
- appropriate and timely switch to second-line ART; and
- ART adherence proxy (ARV refills).

These early warning indicators are included and described in the 2020 WHO consolidated HIV strategic information guidelines *(219,220)*. The results should be used to identify gaps in service delivery, for which corrective actions may be taken at the ART clinic or programme level to optimize overall programme performance.

4.8 Monitoring ARV toxicity

Box 4.6. Guiding principles for monitoring ART toxicity

- The availability of laboratory monitoring is not required for initiating ART.
- Symptom-directed laboratory monitoring for safety and toxicity can be used for those receiving ART.

4.8.1 Major types of ARV toxicity

As in 2016, these guidelines recommend a symptom-directed approach to laboratory monitoring of the safety and toxicity of ART regimens. At the same time, several laboratory tests for monitoring ARV toxicity are advised (but not required) for specific high-risk people using certain drugs. Table 4.13 lists the key types of toxicity and associated risk factors for the major ARV drugs.

Monitoring drug toxicity using a symptom-directed approach needs to be investigated further to optimize treatment outcomes. More data are also needed on whether routine laboratory monitoring for specific types of toxicity (such as renal function monitoring among TDF users or, more recently, weight gain and metabolic monitoring among DTG users (see section 4.5.3) is required for everyone or only those at higher risk of developing the toxicity. In general, in the event of severe and life-threatening toxicity or hypersensitivity, ART should be discontinued until symptoms have resolved and a substitution regimen can be safely initiated.

Chapter 8 provides information on health-systems approaches to monitoring ARV drug toxicity.

Table 4.13 Major types of toxicity associated with first-, second- and third-line ARV drugs

ARV drug	Major types of toxicity	Risk factors	Suggested management
ABC	Hypersensitivity reaction	Presence of *HLA-B*5701* gene	Do not use ABC in the presence of the *HLA-B*5701* gene. Substitute AZT or TDF.
ATV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome	Use with caution for people with pre-existing conduction disease or who are taking concomitant drugs that may prolong the PR or QRS intervals
	Indirect hyperbilirubinaemia (clinical jaundice)	Presence of UDP-glucuronosyltransferase 1-1 enzyme (*UGT1A1*28* gene)	This phenomenon is clinically benign but potentially stigmatizing. Substitute only if adherence is compromised.
	Nephrolithiasis	History of nephrolithiasis	Substitute LPV/r or DRV/r. If boosted PIs are contraindicated and NNRTIs have failed in first-line ART, consider substituting INSTIs
AZT	Anaemia, neutropaenia	Baseline anaemia or neutropaenia CD4 cell count of ≤200 cells/mm3	Substitute TDF or ABC Consider using low-dose AZT
	Lactic acidosis or severe hepatomegaly with steatosis Lipoatrophy, lipodystrophy Myopathy	BMI >25 (or body weight >75 kg) Prolonged exposure to NRTIs	Substitute TDF or ABC

ARV drug	Major types of toxicity	Risk factors	Suggested management
DTG[a]	Hepatotoxicity Hypersensitivity reactions	Coinfection with hepatitis B or C Liver disease	Substitute another therapeutic class: EFV or boosted PIs
	Insomnia Body weight gain or obesityb	Older than 60 years Low CD4 or high viral load Female African ethnicity Concomitant use of TAF	Consider morning dose or substitute EFV, boosted PI or RAL Monitor body weight and promote anti-obesity measures (such as diet and physical exercise). If significant increase despite measures, consider substituting EFV or boosted PI
DRV/r	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	Substitute with ATV/r or LPV/r. When it is used in third-line ART, limited options are available For hypersensitivity reactions, substitute another therapeutic class
	Severe skin and hypersensitivity reactions	Sulfonamide allergy	
EFV	Persistent central nervous system toxicity (such as dizziness, insomnia and abnormal dreams) or mental symptoms (anxiety, depression and mental confusion)	Depression or other mental disorder (previous or at baseline) Daytime dosing	For central nervous system symptoms, dosing at bedtime. EFV 400 mg/day is recommended or an INSTI (DTG) if EFV 400 mg is not effective at reducing symptoms
	Convulsions	History of seizure	
	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	For severe hepatotoxicity or hypersensitivity reactions, substitute another therapeutic class (INSTIs or boosted PIs)
	Severe skin and hypersensitivity reactions	Risk factors unknown	
	Gynaecomastia	Risk factors unknown	Substitute another therapeutic class (INSTIs or boosted PIs)

ARV drug	Major types of toxicity	Risk factors	Suggested management
LPV/r	Electrocardiographic abnormalities (PR and QRS interval prolongation, torsades de pointes)	People with pre-existing conduction system disease Concomitant use of other drugs that may prolong the PR or QRS intervals Congenital long QT syndrome Hypokalaemia	Use with caution for people with pre-existing conduction disease or taking concomitant drugs that may prolong the PR or QRS intervals
	Hepatotoxicity	Underlying hepatic disease Coinfection with hepatitis B or C Concomitant use of hepatotoxic drugs	If LPV/r is used in first-line ART for children, substitute with DTG in children older than four weeks and weighing at least 3 kg. If DTG is not available or tolerated, RAL can be considered as an alternative If LPV/r is used in second-line ART for children, substitute DTG in children older than four weeks and weighing at least 3 kg. If DTG has been used in first line or is not available or tolerated, ATV/r or DRV can be considered as alternatives
	Pancreatitis	Advanced HIV disease, alcohol	Substitute another therapeutic class (INSTIs)
	Dyslipidaemia	Cardiovascular risk factors such as obesity and diabetes	Substitute another therapeutic class (INSTIs)
	Diarrhoea	Risk factors unknown	Substitute atazanavir/r, darunavir/r or INSTIs
RAL	Rhabdomyolysis, myopathy and myalgia	Concomitant use of other drugs that increase the risk of myopathy and rhabdomyolysis, including statins	Stop ART. When symptoms are resolved, substitute another therapeutic class (NNRTIs, boosted PIs)
	Hepatitis and hepatic failure Severe skin rash and hypersensitivity reaction	Risk factor(s) unknown	
TAF	Dyslipidaemia Body weight gain	Female sex Concomitant use of DTG	Monitor body weight and promote anti-obesity measures (such as diet, physical exercise). If significant increase despite measures, consider substituting EFV or boosted PI

ARV drug	Major types of toxicity	Risk factors	Suggested management
TDF	Chronic kidney disease Acute kidney injury and Fanconi syndrome	Underlying renal disease Older than 50 years old BMI <18.5 or low body weight (<50 kg), notably among women Untreated diabetes Untreated hypertension Concomitant use of nephrotoxic drugs or a boosted PI	Substitute AZT or ABC or TAF in special circumstances (see section on using TAF in first-line ART) Do not initiate TDF at an estimated glomerular filtration rate of <50 mL/min, uncontrolled hypertension, untreated diabetes or kidney failure
	Decreases in bone mineral density	History of osteomalacia (adults) and rickets (children) and pathological fracture Risk factors for osteoporosis or bone mineral density loss Vitamin D deficiency	
	Lactic acidosis or severe hepatomegaly with steatosis	Prolonged exposure to nucleoside analogues Obesity Liver disease	

[a] See Box 4.7 on the updates on risk of neural tube defect in neonates exposed to DTG during the first eight weeks of pregnancy.

[b] See section 4.3.8 for special considerations on weight gain associated with INSTIs and evaluation of metabolic consequences.

4.8.2 Safety of DTG during pregnancy

The Guideline Development Group assessed the benefits and risks of using DTG at the time of conception in 2018 and in 2019, reviewing the latest data from Botswana and other countries as well as from modelling the population-level risks and benefits of DTG use among women of childbearing potential as a result of a signal reported in 2018 *(84)*.

The risk of neural tube defects associated with DTG use at the time of conception in the Tsepamo study has progressively declined since the initial report released in May 2018; the rate of neural tube defects appears to have stabilized at 0.19% since September 2019 and is no longer statistically significant when comparing the prevalence of neural tube defects between preconception DTG and preconception non-DTG ART groups *(221–223)* (Box 4.7). Other adverse pregnancy outcomes (miscarriage, stillbirth, preterm birth, low birth weight, small for gestational age and neonatal mortality) were not increased with maternal DTG compared with EFV-containing regimens when the regimens were started preconception or during pregnancy *(221,222)*. There is a continued need to monitor the risk of adverse pregnancy outcomes associated with the use of DTG and other new ARV drugs, and several studies are ongoing to address this *(83,223–225)*. A woman-centred and a rights-based approach should be applied to ART delivery. Concern about the risk of neural tube defects and other pregnancy outcomes has highlighted the importance of both access to reproductive health services, including contraceptives, for women and adolescent girls living with HIV and the importance of the rights of women and adolescent girls living with HIV to make informed choices about their health, including their sexual and reproductive health and choice of ART (see Box 4.2).

Box 4.7. Updates on the risk of neural tube defects among infants born to women receiving DTG before conception or early in pregnancy

The Tsepamo study, a large observational study of birth outcomes that started in 2014 in Botswana, reported in May 2018 a potential association between DTG use and an increased risk of neural tube defects among infants born to the women who were taking DTG at the time of conception. In August 2018, the WHO Advisory Committee on Safety of Medical Products set up a subcommittee on DTG to review all available evidence.

At the last 17th Advisory Committee meeting (27–29 October 2020), data from the Tsepamo study of birth outcomes from May 2018 to April 2020 and other studies were reviewed. The prevalence of neural tube defects with preconception DTG decreased from 0.94% in May 2018 to 0.30% in March 2019 and to 0.19% in April 2020 *(222)*. The prevalence of neural tube defects among infants born to mothers receiving preconception non-DTG regimens remained similar at all time points, between 0.10% and 0.12%; with preconception EFV between 0.05% and 0.07%; and among HIV-uninfected women 0.07% to 0.09%. The difference in the prevalence of neural tube between preconception DTG and preconception non-DTG ART, which was statistically significantly in May 2018 and March 2019, is no longer statistically significant (prevalence difference 0.09%, 95% CI –0.03 and 0.30), although the difference is still borderline higher when the prevalence with preconception DTG is compared with preconception EFV and HIV-uninfected women *(222)*.

The risk of neural tube defects with preconception DTG in the Tsepamo study, should it persist with further increase in the numbers of exposures, appears to be about 0.2% or less, a potential excess of only one neural tube defect per 1000 DTG exposures at conception compared with a general population prevalence of 0.06% in countries with food folate fortification to 0.10% in countries without food folate fortification *(226,227)*. Two separate risk–benefit analyses indicate that the benefits of first-line DTG-based ART compared with EFV-based ART among individuals living with HIV, including women of childbearing potential, significantly outweigh the potential risks *(103,228)*.

WHO strongly supports continuing birth surveillance studies such as the Tsepamo Botswana study, not only to provide a definitive answer to the question of a neural tube defects signal but as a general model for studying the safety of drugs in pregnancy. WHO will update these data and provide additional information as it becomes available.

WHO continues to monitor safety and efficacy data in pregnancy as DTG is scaled up in countries, such as studies in Botswana and Brazil and updates from the Antiretroviral Pregnancy Registry *(225,229,230)*.

WHO recommends both folic acid and iron supplementation for pregnant women, including pregnant women living with HIV, to prevent maternal anaemia, puerperal sepsis, low birth weight and preterm birth *(130)*. The potential protective effects of folic acid supplementation for women of childbearing potential receiving DTG and who wish to become pregnant has not yet been established, but folic acid and iron supplementation during pregnancy have an important role in improving pregnancy outcomes overall.

4.8.3. Monitoring DTG toxicity

An updated systematic review and meta-analysis conducted for these guidelines (a summary report will be made available in the supplementary materials) reported data related to weight gain associated with ART regimens from 35 studies, with most of them reporting data at 48 weeks (28 studies). There was significantly higher weight gain after initiating a DTG + TAF + 3TC or FTC regimen than DTG associated with other ART drug backbones. Initiating DTG-based treatment also led to higher weight increases relative to NNRTI- and elvitegravir/cobicistat-based regimens but was comparable to RAL and bictegravir-based regimens. In reports from clinical trials comparing initiation of DTG- to EFV-based treatment among adults living with HIV, the weight gain observed with DTG was an increase of about 2 kg over 96 weeks and 3 kg at 144 weeks relative to EFV. Greater weight gain with DTG when combined with TAF + 3TC or FTC relative to TDF, ABC and AZT + 3TC or FTC–based ARV drug backbones were more consistent between studies, since TAF led to higher weight gain relative to all comparison drugs. The relative weight gains observed with use of TAF-based drug backbone versus TDF and AZT-based drug backbones increased consistently over time, reaching differences of 4 kg and 5 kg at 144 weeks relative to TDF and AZT-based drug backbones, respectively. Both low CD4 and high HIV RNA were highly prognostic of higher weight gain, while the effects of sex on weight gain appear to be ethnicity dependent, with higher rates among African women compared with men. Reporting on serious adverse events of hyperglycaemia or diabetes was limited across studies and did not enable analysis. An expert think-tank convened by WHO in March 2020 concluded that more data were required to better document long-term body weight gains with DTG with and without TAF, including in different populations and geographical regions and how this relates to metabolic consequences *(132)*. Box 4.8 describes the community perspectives on newer drugs and the associated risk of toxicity.

Specific considerations on DTG and weight gain in pregnancy

Unsuppressed viral load is the strongest risk factor for mother-to-child HIV transmission and adverse maternal and child clinical outcomes. Thus, the rapid scale-up of DTG to women living with HIV who are pregnant has the potential to further reduce mother-to-child HIV transmission and improve pregnancy outcomes in low- and middle-income countries, where the burden of HIV is greatest (see section 4.6.1). However, the effect of INSTIs, including DTG, on gestational weight gain and pregnancy outcomes is only beginning to emerge *(231).*

The Tsepamo birth outcomes surveillance study in Botswana evaluated the relationship between maternal weight (and weight gain) and adverse birth outcomes *(232)*. Interestingly, the results showed that baseline weight was more strongly associated with adverse outcomes than weight gain during pregnancy and that low baseline weight (<50 kg) was associated with increased risk of very preterm delivery (<32 weeks) and very small for gestational age (<3rd percentile) infants. High baseline weight (>90 kg) was associated with increased risk of macrosomia (birth weight >4000 g) and maternal hypertension. Baseline weight was not associated with perinatal death. Although DTG-based ART was associated with greater gestational weight gain than EFV-based ART, women receiving DTG-based ART had lower gestational weekly weight gain than pregnant women without HIV infection and below the second and third trimester gestation weekly weight gain recommended in pregnancy by the Institute of Medicine *(232)*. The investigators also reported that the risk of maternal hypertension was higher among pregnant women receiving DTG compared with EFV regimens across all baseline weight categories *(233)*. However, although gestational hypertension was more common among women on DTG at conception than women on EFV at conception, it was less common than among women without HIV.

The VESTED study evaluated initiation of DTG ART, combined with either a TAF or TDF-based backbone, to EFV + TDF + FTC among pregnant women after the first trimester of pregnancy. DTG-based combinations had superior antiviral efficacy at delivery. Low weight gain was most common with EFV-based ART, and low weight gain was associated with a higher risk of any adverse pregnancy outcome and small-for-gestational-age infants *(234)*. DTG-based ART, especially DTG + TAF + FTC versus DTG + TDF + FTC, was associated with higher weight gain than EFV-based ART, but none of the study arms had weight gain that met the Institute of Medicine–recommended weight gain in later pregnancy. There were no associations between high gestational weight gain and adverse pregnancy outcomes or low or high gestational weight gain and neonatal death.

Clinical considerations

The following are useful to consider:

- adequate counselling on lifestyle and dietary changes for everyone gaining weight;
- using routine blood pressure to assess for hypertension, with special attention to the risk of hypertension during pregnancy;
- monitoring and treating metabolic parameters – glucose and lipid monitoring when routinely available; and
- monitoring weight and associated complications as part of routine or active toxicity monitoring (see Fig. 8.2) *(235)*.

Box 4.8. Community perspectives on newer drugs and the associated risk of toxicity

Community perspectives on newer ARV drugs enable decision-makers to tailor guideline recommendations to place and person – and to improve the applicability of programmes in certain settings. Some of the concerns brought forward concerned the safety of using DTG among women of childbearing potential. It was reported that some women younger than 35 years are not receiving DTG and are being asked to stay on regimens based on EFV 600 mg. This is a cause for concern, since ensuring an adequate supply of EFV 600 mg in the future, the existing high pretreatment levels of drug resistance to NNRTIs and inequity of the efficacy of ART are key issues that need to be addressed and also highlight that assuring reliable contraception remains a challenge in many countries.

The HIV community strongly desires to have access to a DTG-based regimen in preference to EFV 600 mg; this preference extends to EFV 400 mg, which has demonstrated better tolerability than EFV 600 mg. It was concluded that some of this attitude could be from having previously taken EFV 600 mg. The results of the session discussion *(132)* also included the expectation to identify alternatives to DTG for people who are unable to take this product and reiterated the need to review and update the HIV drug pipeline. Among other new ARV drug options, doravirine emerged as a possible candidate. There is, however, very limited information on the efficacy of doravirine, especially for children, pregnant women and those with high plasma viral load. Doravirine also cannot be used together with TB regimens containing rifampicin. The need for examining potential alternative regimens is indicated, especially those currently early in development.

More research is needed with communities and advocacy groups to understand the metabolic, other health and social implications of potential weight gain. The early response from communities and women enrolled in studies who experienced weight gain while taking DTG was that weight gain is largely a viewed as a favourable outcome but that they desired further information on the potential health implications as this becomes more available. The groups clearly emphasized adequate counselling and support on the potential weight gain.

Research gaps

Research is required to further determine the mechanisms associated with body weight gain with receiving DTG-based regimens and/or TAF, whether this is reversible, key risk factors and the effects of weight gain on metabolic consequences, including hyperglycaemia and cardiometabolic morbidity. More research is needed across multiple regions; Asian countries, for example, have observed little evidence for metabolic complications with DTG treatment. Further investigation into the risks of weight gain among adolescents and children receiving DTG-based ART is also needed.

Toxicity surveillance systems implemented alongside ART can provide data to better understand the frequency and clinical relevance of various types of toxicity *(236)*. Assessing the safety of ARV drugs on birth defects and other adverse pregnancy outcomes (miscarriage, stillbirth, preterm birth, low birth weight, small for gestational age, stillbirth and neonatal mortality) remains important.

Further research is needed to inform the extent and clinical effect of INSTI-based ART on baseline weight at pregnancy as well as gestational weight gain and subsequent pregnancy outcomes among women living with HIV; the association with the potential risk of cardiometabolic complications in pregnancy, including hypertensive disorders and gestational diabetes, relative to other regimens and among women not infected with HIV; the long-term cardiometabolic risk for women living with HIV and their children exposed to HIV and ART; and the identification of optimal screening, treatment and behavioural interventions for weight gain. Continued surveillance of birth outcomes among pregnant women receiving ART, especially in the periconception period, is critical. There is a large research gap on the safety and efficacy of DTG (and other new ARV drugs) among transgender people in terms of drug–drug interactions.

More evidence is needed to assess pregnancy outcomes with periconception and during pregnancy exposure to TAF. The role of TAF on body weight gain and some cardiometabolic events, especially when used with DTG and other INSTIs, needs to be further evaluated *(132)*.

4.8.4 Monitoring the toxicity of ARV drugs among adolescents, children and neonates

Optimizing the safety and tolerability of ARV drug regimens for treating adolescents, children and neonates living with HIV is critical to ensuring durability of treatment and quality of care. An updated systematic review conducted in 2021 confirms that DTG has a good tolerability profile with no drug discontinuation, no grade 3 or 4 or adverse drug reactions and no deaths reported across the studies in which DTG was used as first-line ART *(99,237)*.

In particular, a randomized controlled trial investigating the use of DTG versus the standard of care showed better lipid profile (with lower total cholesterol) and marginal increase in weight, height and BMI at 96 weeks. To date, programme data from countries where rapid transition to DTG is occurring have not reported any toxicity or tolerability concerned *(127,128)*. Although all these findings are very reassuring, the use of DTG is still relatively limited, and routine active monitoring is needed as good practice for all new ARV drugs in these populations.

4.8.5 Drug substitutions for ARV drug toxicity

Drug regimen or single-agent substitutions may be required to manage drug toxicity and to avoid drug–drug interactions. Delaying substitutions or switches when there are severe adverse drug reactions may cause harm and may affect adherence, leading to drug discontinuation, resistance and treatment failure.

When drug interruptions are required, such as for severe and life-threatening adverse reactions, it is important to consider the various half-lives of ARV drugs. For example, when an NNRTI needs to be discontinued, a staggered approach should be followed, in which the use of the NRTI backbone is prolonged for two to three weeks. Alternatively, the NNRTI could be temporarily replaced with a boosted PI. (see Table 4.14 and section 4.5.2).

Table 4.14 Key ARV drug–drug interactions and suggested management

ARV drug	Key interactions	Suggested management
TAF	Rifampicin	TAF 25 mg once daily may still provide sufficient concentrations of intracellular tenofovir diphosphate
TDF	Ledipasvir- or velpatasvir-containing regimens	Monitor for TDF-associated adverse effects, including renal dysfunction, particularly when TDF is co-prescribed with boosted HIV PIs
	Lithium	TDF: monitor renal function closely
Boosted PI (ATV/r, DRV/r, LPV/r)	Rifampicin	Replace rifampicin with rifabutin Adjust the dose of LPV/r or substitute three NRTIs (for children)
	1HP or 3HP	Avoid the combination Consider alternative ARV drugs such as EFV + DTG Consider a non-rifamycin-based approach, such as daily isoniazid
	Bedaquiline or delamanid	Use with caution as there is a risk of QT prolongation
	Lumefantrine	Potential for increased lumefantrine exposure Risk of QT prolongation with ATV/r and LPV/r
	Methadone and buprenorphine	Adjust methadone and buprenorphine doses as appropriate
	Quetiapine	If co-administration is unavoidable, use quetiapine at one sixth the normal dose
	Pimozide	Avoid this combination because of the risk of serious arrhythmia; use alternative ARV drugs or antipsychotic drugs
	Lithium, haloperidol, fluphenazine	Use with caution since there is a risk of QT prolongation with ATV/r and LPV/r
	Amlodipine	Consider reducing the dose of amlodipine by 50%
	Antidiabetic drugs (such as glibenclamide and gliclazide)	Adjust the antidiabetic drug dose as appropriate
	Statins	Simvastatin: contraindicated because of the risk of rhabdomyolysis; use alternative dyslipidaemia agent Atorvastatin: dose adjustment required; total daily dose should be limited to 10 mg with ATV/r, 40 mg with DRV/r and 20 mg with LPV/r
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Fluticasone or budesonide	Risk of Cushing's syndrome; use alternative corticosteroid (such as beclomethasone)
	Acid-reducing agents	ATV/r: use at least 2 hours before or 1 hour after antacids; contraindicated with proton pump inhibitors

ARV drug	Key interactions	Suggested management
DTG	Carbamazepine, phenobarbital and phenytoin	Use an alternative anticonvulsant agent (such as valproic acid or gabapentin)
	Rifampicin	Increase DTG to 50 mg twice daily; avoid in the presence of integrase class resistance. Continue with twice daily dosing of DTG in children for 2 weeks after use of rifampicin has ended
	Rifapentine in TB preventive treatment regimens (1HP or 3HP)	No evidence that change of dose of rifapentine or DTG is needed to achieve adequate exposures of DTG
	Metformin	Avoid high-dose metformin with DTG; adjust the metformin dose as appropriate
	Polyvalent cation products containing Mg, Al, Fe, Ca and Zn	Use DTG at least two hours before or at least six hours after supplements containing polyvalent cations, including but not limited to the following products: Fe-, Ca-, Mg- or Zn-multivitamin supplements; mineral supplements, cation-containing laxatives and Al-, Ca- or Mg- containing antacids. Monitor for antiviral efficacy
RAL	Carbamazepine, phenobarbital and phenytoin	Use alternative anticonvulsant agent (such as valproic acid or gabapentin).
	Rifampicin	Increase RAL to 800 mg twice daily (RAL 400 mg twice daily can be used with 3HP). Continue with twice daily dosing of RAL in children for 2 weeks after use of rifampicin has ended
	Rifapentine in TPT regimens (1HP or 3HP)	No evidence that change of dose of rifapentine or RAL is needed to achieve adequate exposures of RAL
	Antacids	Al- or Mg-containing antacids – not recommended Ca-containing antacids – not recommended with RAL once daily; no dose adjustment with RAL twice daily
	Ca-, Fe- and Mg-containing supplements or multivitamins	RAL twice daily: separate intake by at least four hours RAL once daily: not recommended
EFV	Bedaquiline	Avoid the combination
	Amodiaquine, DHA/piperaquine	Use an alternative antimalarial agent or substitute EFV for DTG
	Artemisinins or lumefantrine	Use an alternative antimalarial agent or substitute EFV for DTG Risk of QT prolongation with ATV/r and LPV/r
	Methadone	Adjust the methadone dose as appropriate
	Quetiapine	Adjust the quetiapine dose as appropriate
	Hormonal contraceptives	Use alternative or additional contraceptive methods
	Amlodipine	Adjust the amlodipine dose as appropriate
	Simvastatin and atorvastatin	Adjust the statin dose as appropriate
	Low-dose dexamethasone (COVID-19)	Double dose of dexamethasone

ARV drug	Key interactions	Suggested management
NVP	Rifampicin	Replace NVP with EFV
	HCV NS3/4A protease inhibitors	Use alternative HCV direct-acting antiviral drug regimen
	Quetiapine	Adjust the quetiapine dose as appropriate
	Amlodipine	Adjust the amlodipine dose as appropriate
	Simvastatin	Adjust the simvastatin dose as appropriate
	1HP or 3HP	Avoid the combination. Consider a non-rifamycin-based approach, such as daily isoniazid or an alternative ARV drug such as EFV + DTG
	Low-dose dexamethasone (COVID-19)	Double dose of dexamethasone

This table was developed using the University of Liverpool's drug interaction charts *(238)*. A more comprehensive table of ARV drug interactions is available in the annexes.

4.9 ARV drug resistance

Public health response to pretreatment HIV drug resistance

A high prevalence of pretreatment HIV drug resistance to NNRTIs negatively affects the success of the public health response to HIV and potentially endangers the attainment of the global target to end the AIDS epidemic as a global threat.

In 2017, WHO published guidelines on the public health response to pretreatment HIV drug resistance to NNRTIs among people without previous ARV drug exposure or people with previous ARV exposure who are initiating or reinitiating first-line ART *(78)*. The guidelines also provided the consensus prevalence or threshold of pretreatment HIV drug resistance to NNRTIs at which specific public health actions are triggered *(78)*.

These recommendations support countries in responding to pretreatment HIV drug resistance to NNRTIs to attain and maintain the treatment target of 95% suppression of viral loads among all people receiving first-line ART by 2025 *(239)* and address the first strategic objective of the WHO Global Action Plan on HIV drug resistance 2017–2021 *(240)* on the prevention and response to HIV drug resistance.

Prevalence of pretreatment HIV drug resistance

The 2019 WHO report on HIV drug resistance shows that levels of pretreatment HIV drug resistance to NNRTIs are high in most of the countries surveyed *(85)*. Nationally representative surveys from 18 low- and middle-income countries conducted in 2014–2018 among people initiating first-line ART show a high prevalence of pretreatment HIV drug resistance to NNRTIs, reaching 10% or above in 12 of 18 countries: Argentina, Cuba, Eswatini, Guatemala, Honduras, Namibia, Nepal, Nicaragua, Papua New Guinea, South Africa, Uganda and Zimbabwe *(85)*.

In Africa, the prevalence of NNRTI resistance was greater than 10% in four of six countries reporting data to WHO, with pretreatment HIV drug resistance to EFV + NVP ranging from 8% in Cameroon to 21% in South Africa *(85)*. In the Americas, pretreatment NNRTI resistance exceeded 10% in five of eight countries and ranged from 6% in Colombia to 26% in Honduras *(85).* In South-East Asia and the western Pacific, pretreatment NNRTI resistance exceeded 10% in two of four countries: 10% in Nepal and 18% in Papua New Guinea *(85).*

Pretreatment HIV drug resistance to NNRTIs was shown to be significantly higher among individuals initiating first-line ART with previous ARV drug exposure (such as women who had received ARV drugs solely to prevent mother-to-child HIV transmission and people restarting ART after a period of treatment interruption) compared with ARV drug–naive ART initiators in all WHO regions. These findings are also consistent with the systematic review assessing the prevalence of pretreatment HIV drug resistance globally *(110).*

Clinical impact of pretreatment HIV drug resistance

A systematic review and meta-analysis conducted to inform the development of these guidelines showed that individuals with pretreatment resistance are more likely to experience virological failure (OR 3.07, 95% CI 2.40–3.94); the increased risk was observed both for adults (OR 2.78, 95% CI 2.19–3.53) and children (OR 7.47, 95% CI 2.12–26.41) *(241)*. In sensitivity analysis restricted to 10 studies only focusing on NNRTI pretreatment HIV drug resistance among adults, it was associated with an even more pronounced risk of virological failure (OR 4.26, 95% CI 2.55–7.12) *(241)*. In addition, new resistance mutations were more likely to emerge among people taking NNRTI-based first-line ART who had pretreatment HIV drug resistance when initiating treatment compared with those without (OR 2.45, 95% CI 1.70–3.52). People with pretreatment HIV drug resistance were more likely to discontinue or switch ART than people without (OR 3.25, 95% CI 1.86–5.67) *(241)*.

To address concerns about the observed high prevalence of pretreatment HIV drug resistance to NNRTIs and how it affects treatment outcomes, WHO is strengthening its response to HIV drug resistance through these guidelines and broader efforts described in the Global Action Plan on HIV drug resistance *(240)*.

The Guideline Development Group convened by WHO expressed concern about the increasing prevalence of pretreatment HIV drug resistance in low- and middle-income countries and agreed that urgent public health action is needed in countries with a high prevalence of pretreatment HIV drug resistance to NNRTIs.

The Guideline Development Group made the following recommendations and consensus statement *(78)*.

- **For people initiating first-line ART with pretreatment HIV drug resistance to NNRTIs, a NNRTI-containing regimen should be avoided** *(conditional recommendation, low-certainty evidence).*
- In countries in which the prevalence of pretreatment HIV drug resistance to NNRTIs among people initiating first-line ART is equal to or greater than 10%, NNRTI-based ART should be avoided (consensus statement).

The Guideline Development Group formulated a consensus statement specifying the threshold for pretreatment HIV drug resistance to NNRTIs that should trigger a public health response. The consensus statement was formulated in a transparent process following a framework developed by the methodologist and the WHO Steering Group that considered the current and historical data on the prevalence of pretreatment HIV drug resistance, the results from the

systematic review showing how pretreatment HIV drug resistance affects treatment outcomes, modelling data and acceptability and feasibility *(78)*.

DTG is recommended as the preferred first-line ART. However, in settings and populations in which DTG-based ART is not available or unsuitable because of toxicity, the following considerations are inferred from the 2017 WHO guidelines on the public health response to pretreatment HIV drug resistance *(78)*.

In settings with a high prevalence of pretreatment HIV drug resistance to NNRTIs, boosted PI/r-based ART should be considered in first-line ART in circumstances in which DTG is unavailable or unsuitable because of toxicity considerations (Table 4.1) *(79)*.

Because of programmatic considerations, safety in pregnancy and HIV drug resistance profile, ATV/r or DRV/r appear to have advantages compared with LPV/r, although the data are limited and recommendations on the choice of PI could not be made.

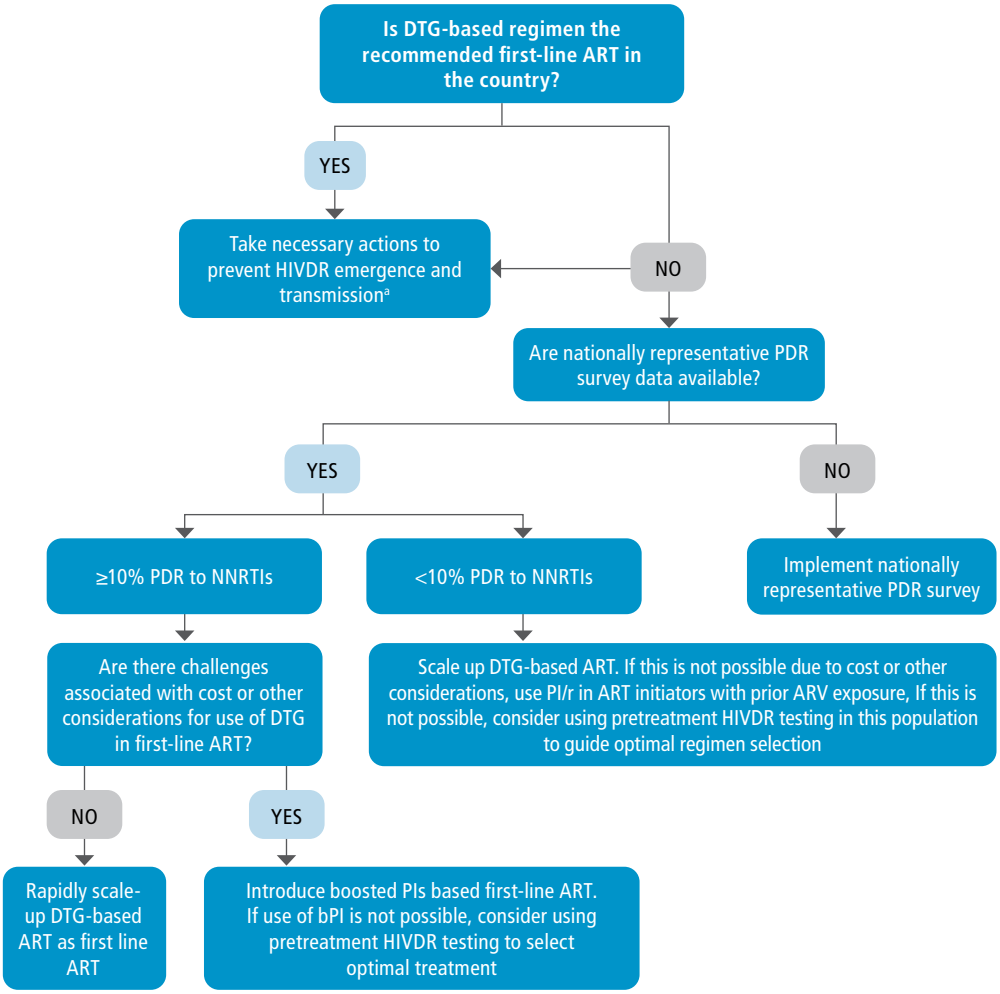
Alternatively, HIV drug resistance testing should be considered where feasible to guide first-line ART regimen selection in settings with no access to DTG-based ART and in which the national prevalence of pretreatment HIV drug resistance to NNRTIs is equal to or greater than 10% (Fig. 4.3, Table 4.1) *(78).*

The Guideline Development Group considered additional important factors for people reinitiating ART with reported previous exposure to NNRTIs in settings in which DTG-based ART is not available or suitable.

People initiating or reinitiating ART with reported previous exposure to NNRTIs have a significantly higher risk of pretreatment HIV drug resistance to NNRTIs than people who are ARV-naive *(85,110)*. In this population, an NNRTI-containing regimen is not recommended, regardless of the country's prevalence of NNRTI pretreatment HIV drug resistance and without the need to document whether the individual has NNRTI resistance by using an HIV drug resistance test.

In settings in which DTG is unavailable or in populations in which DTG is unsuitable, people initiating ART with reported previous exposure to NNRTIs should start PI/r-based ART or should receive pretreatment HIV drug resistance testing, where feasible, to select an optimal first-line regimen *(78).*

Fig. 4.3 WHO's recommended response to pretreatment HIV drug resistance to NNRTIs



[a] See section 4.7

Source: *Guidelines on the public health response to pretreatment HIV drug resistance: July 2017 (78).*

4.10 Key ARV drug interactions

Drug interactions can reduce the efficacy of ART and/or increase ART-related toxicity. This section summarizes the major ARV drug interactions. A detailed table on drug interactions is available in the annexes.

Pharmacokinetic drug–drug interactions can reduce the efficacy of ART and/or increase ART-related toxicity. Common pitfalls include co-administering PIs with potent corticosteroids (especially inhaled ones, such as budesonide and fluticasone, or locally injected ones, such as triamcinolone), which can increase the risk of developing Cushing's syndrome; ATV/r with acid-reducing agents (antacids and proton pump inhibitors), which can significantly reduce ATV concentrations; or PIs with simvastatin, which can cause rhabdomyolysis. Major ARV drug interactions are summarized in Table 4.14 and described in more detail in the annexes. Health-care providers should be aware of all drugs – including alternative medicine products such as herbal remedies and dietary supplements – people are taking when ART is initiated as well as new drugs that are added during treatment maintenance.

TB

WHO TB treatment guidelines include key considerations for managing concomitant TB and ART for the prevention of HIV-associated TB, drug-susceptible TB and multidrug-resistant-TB *(59)*. Key contraindicated drug combinations include rifampicin with PIs or NVP. When people with both HIV and TB are receiving a boosted PI, rifampicin may need to be replaced by rifabutin at a daily dosage of 150 mg. If rifabutin is not available, LPV/r can be used for the duration of TB treatment by doubling the standard dose of LPV/r or increasing the boosting dose of RTV (see section 4.8.1). When rifampicin is used with DTG, the dosage should be raised to 50 mg twice daily in the absence of INSTI resistance, otherwise this combination should be avoided. When used in children, twice daily dosing of DTG or RAL should be provided for an additional two weeks after use of rifampicin has ended. If the use of RAL is considered (only under special circumstances), a doubling of the dosage to 800 mg twice daily is indicated since recent evidence shows that standard doses of RAL with rifampicin do not meet non-inferiority criteria *(242)*. Rifampicin reduces TAF and tenofovir exposure, but recent data showed that the intracellular tenofovir diphosphate (active entity) levels were still fourfold higher than those obtained with TDF even without rifampicin *(81)*, suggesting that using TAF 25 mg once daily with rifampicin may be acceptable when TAF is considered in first-line ART (only under special circumstances).

Currently, there are no virological outcome data for either TAF 25 mg once daily or twice daily with rifampicin. In people with HIV and extensively drug-resistant or multidrug-resistant TB receiving drugs for drug-resistant TB such as bedaquiline and delamanid, caution should be exercised when co-administering with PIs because of the risk of QT-interval prolongation. Further, since bedaquiline is primarily metabolized by CYP3A4, concomitant use with EFV can reduce bedaquiline drug concentrations, resulting in potential loss of activity and therefore this association should be avoided. Treatment of latent TB infection with 1HP or 3HP is not recommended for people receiving PIs or NVP because of the risk of HIV virological failure. At this point there is no evidence to indicate that a change of dosage of rifapentine and DTG or RAL is needed in patients on 1HP or 3HP. Similar to rifampicin, DTG, RAL and TAF dosage needs to be doubled with 1HP, whereas their standard dose can be used with 3HP (see section 4.4.1). Details of drug–drug interactions with 3HP are available in the prescribing resources section of the HIV drug interaction website of the University of Liverpool *(238)*, Chapter 6 summarizes current WHO guidance on management of HIV-associated TB.

Malaria

WHO recommends artemisinin-based combination therapies for treating uncomplicated *Plasmodium falciparum* malaria *(243)*. EFV is a moderate inducer of cytochrome P450 metabolism and is known to significantly lower plasma concentrations of artemisinins, thus increasing the risk of suboptimal treatment of malaria. In one study, concentrations of artemether and its active metabolite DHA were approximately halved by EFV; lumefantrine concentrations were reduced by 20%. This was associated with a fourfold higher risk of recurrent malaria at day 28 among children in Uganda compared with those receiving LPV/r-based regimens *(243)*. EFV is also expected to reduce piperaquine concentrations, and combining DHA and piperaquine is not recommended. A healthy volunteer study was discontinued after two subjects receiving EFV and amodiaquine developed symptomatic elevation of liver transaminases – this combination is not recommended.

LPV/r significantly increases lumefantrine exposure, but the clinical relevance of this is unknown. However, since both drugs tend to increase the QT interval on the electrocardiogram (albeit for a relatively short duration of treatment of malaria), caution is advised when co-administering these drugs. In contrast, DTG is not associated with significant risk for drug–drug interactions with any WHO-recommended artemisinin-containing regimen.

Hepatitis C

Potential drug–drug interactions should be considered when using ARV drugs and direct-acting antiviral agents for HCV infection. Ledipasvir and velpatasvir with sofosbuvir have shown reduced potential for drug–drug interactions with ARV drugs because they use different metabolic pathways *(244,245).* However, they may increase TDF exposure because of permeability glycoprotein inhibition, and caution is warranted, especially when TDF is used in combination with boosted PIs. Grazoprevir- and glecaprevir-containing regimens are contraindicated with ATV and DRV. Hepatitis C direct-acting antiviral agents do not interact with other NRTIs or unboosted INSTIs.

Opioid substitution therapy

WHO recommends methadone or buprenorphine for treating opioid dependence *(246)*. Co-administering EFV decreases methadone and buprenorphine concentrations. This could subsequently cause withdrawal symptoms and increase the risk of relapse to opioid use. People taking methadone and EFV should be monitored closely, and those experiencing opioid withdrawal may need to adjust their methadone dose. LPV/r may also reduce concentrations of methadone, and both drugs are associated with QT prolongation.

Mental health

Medications used in treating mental health conditions have often been carefully titrated to achieve an equilibrium of efficacy versus toxicity, and co-administering them with ARV drugs requires carefully managing drug–drug interactions. Quetiapine should not be used in combination with PIs unless absolutely necessary and if so, at one sixth the normal dose. The enzyme-inducing NNRTIs, EFV and NVP may decrease levels of quetiapine, risking suboptimal effects and destabilizing the clinical effect. Pimozide is contraindicated with PIs, since they may increase pimozide concentrations, which may result in serious or life-threatening reactions such as cardiac arrhythmia. Many agents for treating mental health conditions can prolong the heart rate–corrected QTc interval, including lithium, haloperidol or fluphenazine, and caution is required in combination with PIs. No pharmacokinetic interactions occur with NRTIs or unboosted integrase inhibitors.

Hormonal contraceptives and high-dose hormonal therapy for gender affirming

ARV drugs have the potential to either decrease or increase the levels of steroid hormones in hormonal contraceptives *(247)*. EFV can reduce contraceptive efficacy (including implant, vaginal ring and transdermal contraceptives), and a reliable method of barrier contraception must therefore be used in addition to hormonal contraceptives to prevent unintended pregnancy. For women requiring emergency contraception while taking EFV, a copper intrauterine device is preferred. Alternatively, a single dose of 3 mg of levonorgestrel can be used. RTV-boosted PIs can reduce the estrogen component and therefore caution is recommended and additional contraceptive measures should be used. NRTIs, newer NNRTIs and unboosted integrase inhibitors do not interact with hormonal contraceptives (see the annexes). The contraceptive efficacy of injectable formulations of either intramuscular or subcutaneous depo-medroxyprogesterone acetate (DMPA) is unaffected by ARV drugs, and it can be used without restrictions *(248).* WHO has made recommendations on the use of hormonal contraception by women receiving ART *(247).*

High-dose hormonal therapy for gender transitioning does not alter the efficacy of ARV drugs. DTG, RAL, newer NNRTIs and NRTIs do not interact with hormones for gender transitioning, but hormones need to be adjusted with PIs, EFV and NVP. Dosage recommendations for hormone therapy for gender affirming are available in the prescribing resources section of the HIV drug interaction website of the University of Liverpool *(238).*

Cardiovascular

PIs increase the concentrations of the antihypertensive drug amlodipine, and a 50% dose reduction should therefore be considered. Dosage may also need to be adjusted when administering antidiabetic drugs (glibenclamide and gliclazide) with PIs. Metformin does not interact with PIs, but its exposure increases with DTG. Adjusting the dose of metformin should be considered when starting or stopping DTG to maintain glycaemic control. High doses of metformin should be avoided and close monitoring of people with moderate renal impairment is recommended.

WHO recommends statins for people with a 10-year cardiovascular risk exceeding 30% *(249).* Boosted PIs are contraindicated with simvastatin because of the risk of rhabdomyolysis. Atorvastatin can be used with PIs, but the total daily dose should be limited to 10 mg with ATV/r, 40 mg with DRV/r and 20 mg with LPV/r. An increase in atorvastatin dose may be needed with EFV and NVP. Statins do not interact with DTG, RAL or NRTIs.

COVID-19

Dexamethasone is used at doses ranging from 6 mg up to 20 mg daily for short duration for people with COVID-19. At such doses, dexamethasone has a weak to moderate inducing effect that does not warrant any dose adjustment of EFV, NVP, PIs, DTG or RAL. Conversely, EFV and NVP may decrease dexamethasone concentrations, and doubling of the dexamethasone dose is therefore recommended. No drug–drug interactions are expected between ARV drugs and the COVID-19 vaccines.

Other interactions

DTG should not be simultaneously administered with cation-containing antacids, laxatives and multivitamin or mineral supplements because of the risk of chelation. If combined, DTG should be administered two hours before or six hours after taking medications containing polyvalent cations *(250).*

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MANAGING ADVANCED HIV DISEASE

05

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5. MANAGING ADVANCED HIV DISEASE

This chapter summarizes guidance on managing people presenting for health care with advanced HIV disease. For the full set of guidelines, please see WHO's previous guidelines for managing advanced HIV disease *(1)*.

5.1 Introduction

In 2015, WHO recommended that all people living with HIV start ART irrespective of clinical or immune status. Most national guidelines have adopted this recommendation *(2)*. However, despite this progress, up to half the people living with HIV continue to present to care with advanced HIV disease.

WHO defines advanced HIV disease for adults and adolescents (and children five years and older) as having a CD4 cell count of less than 200 cells/mm^3 or WHO clinical stage 3 or 4 disease *(3)*. All children younger than five years living with HIV are considered to have advanced HIV disease.

Children older than two years who have been receiving ART for more than one year and are clinically stable should not be considered to have advanced disease and should be eligible for multimonth ART dispensing (subsection 5.6).

Advanced HIV disease includes people presenting to care for the first time following an HIV diagnosis and people who have treatment failure and consequent decline in CD4 cell count. Individuals who had previously initiated ART and are re-engaging with care after a period of ART interruption should be assessed for advanced HIV disease and should be offered the advanced HIV disease package as appropriate.

People presenting with advanced HIV disease are at high risk of death, even after starting ART, with the risk increasing with decreasing CD4 cell count, especially with CD4 cell count <100 cells/mm^3 *(3–6)*. Advanced HIV disease is also associated with increased health-care costs *(7)*, increased risk of opportunistic infections, immune reconstitution inflammatory syndrome, incomplete immune reconstitution, higher viral reservoirs, higher inflammation, increased risk of AIDS-related and non-AIDS-related comorbidities, use of more health-care services and more frequent monitoring needs.

5.2 Causes of morbidity and mortality among adults with advanced HIV disease

Leading causes of mortality among adults with advanced HIV disease globally include TB, severe bacterial infections, cryptococcal disease, histoplasmosis, toxoplasmosis and *Pneumocystis jirovecii* pneumonia. Other invasive fungal infections have been recently estimated as contributing significantly to the number of people dying from AIDS-related causes *(8)*.

TB

TB is the leading cause of morbidity and mortality among people living with HIV *(9)*. In 2019, an estimated 1.2 million (range, 1.1 million–1.3 million) HIV-negative people died from TB (a reduction from 1.7 million in 2000), and an additional 208 000 HIV-positive people died from TB (range, 177 000–242 000) (a reduction from over 678 000 in 2000) *(10)*. TB also remains a leading cause of HIV-associated hospitalization among adults and children living with HIV worldwide *(11)*. See section 6.5 for more information on managing people coinfected with TB and HIV.

Severe bacterial infections

People with advanced HIV disease frequently have severe bacterial infections, including bloodstream, respiratory, central nervous system and gastrointestinal infections *(12)*. The burden of mortality and morbidity attributable to severe bacterial infections is poorly characterized, largely because appropriate diagnostic testing facilities are lacking. Severe bacterial infections are estimated to cause more than one third of the hospitalizations among adults and children living with HIV worldwide *(13)*.

Invasive fungal infections

Cryptococcal disease

By far the most common presentation of cryptococcal disease is cryptococcal meningitis, which accounts for an estimated 15% of all people dying from AIDS-related causes globally, three quarters of which are in sub-Saharan Africa *(14)*. Less common presentations of cryptococcal disease include pulmonary disease, skin, lymph node and bone involvement. Cryptococcal disease is less common among young children than among adults. Subsection 5.4 provides more details about managing cryptococcal disease among people with advanced HIV disease.

Histoplasmosis

Histoplasmosis is a fungal disease mostly reported in the WHO Region of the Americas, but it has also been reported in countries in Asia and Africa *(15)*. Histoplasmosis is highly endemic in some regions of Central and South America and is a major opportunistic infection among people living with HIV *(15)*. Thousands of people living with HIV with advanced disease are estimated to die from histoplasmosis each year *(8)*. A major concern about histoplasmosis is misdiagnosing it as TB and the high frequency of co-occurrence (about 20%) because of lack of rapid and accurate diagnosis *(16)*. Subsection 5.5 provides more details about managing histoplasmosis among people with advanced HIV disease.

Pneumocystis jirovecii pneumonia

Pneumocystis jirovecii pneumonia is a leading cause of mortality among hospitalized adults (13%) and children (29%) living with HIV *(13)*. However, the global burden of morbidity and mortality attributable to *P. jirovecii* pneumonia is poorly characterized because appropriate diagnostic testing facilities are lacking in most settings.

Toxoplasmosis

Cerebral toxoplasmosis is the most frequent cause of expansive brain lesions among adults living with HIV not receiving co-trimoxazole. Toxoplasmosis is a common protozoan infection among people with HIV, with the prevalence of coinfection especially high in sub-Saharan Africa (45%), Latin America and the Caribbean (49%) and North Africa and the Middle East (61%) *(17)*. People with latent toxoplasmosis infection are at risk of developing cerebral toxoplasmosis when their CD4 count falls below 200 cells/mm^3.

Other important fungal infections

Fungal infections other than those caused by *Cryptococcus* species and *P. jirovecii*, notably histoplasmosis and talaromycosis, are associated with advanced HIV disease in specific geographical areas.

Talaromycosis (formerly known as penicilliosis) is a systemic mycosis that is endemic to many countries in South-East Asia, including parts of China and India, and is a leading cause of HIV-associated mortality, especially among individuals with a CD4 cell count <100 cells/mm^3. Untreated disseminated infection is usually fatal, and even when appropriate therapy is provided mortality rates among hospitalized people are up to 30% *(18,19)*.

Emergomycosis and other dimorphic fungal pathogens are emerging around the world. The emergence of novel species, such as *Emergomyces africanus*, is adding challenges to the clinical care of immunocompromised people, including those with advanced HIV disease *(20)*. Lack of knowledge about diagnosis, treatment and care are key aspects for further work.

Cytomegalovirus disease

Cytomegalovirus infection is a systemic viral infection that usually manifests as cytomegalovirus retinitis among severely immunocompromised people; the reported prevalence of cytomegalovirus retinitis is highest in Asia and appears to be low in Africa *(21)*.

Wasting syndrome and malnutrition

Malnutrition and wasting are an important cause of hospitalization, responsible for 3% of hospitalizations overall, rising to 12% in the WHO African Region *(13)*. Nutritional assessment (anthropometry and clinical and dietary assessment), counselling and support should be an integral component of HIV care and conducted at enrolment in care and monitored across the care continuum. Children with advanced HIV disease commonly present with malnutrition.

Assessing advanced HIV disease

CD4 cell count is the best indicator of disease stage and immediate risk of death and thus should be used to identify people with advanced HIV disease. If access to CD4 count is limited or unavailable, WHO staging should be used. For children from five years of age, adolescents and adults, advanced HIV disease is defined as the presence of a CD4 cell count <200 cells/mm^3 or WHO clinical stage 3 or 4. All children younger than five years (who are not already receiving ART and clinically stable) are considered to have advanced HIV disease.

Everyone entering or re-entering care should receive a CD4 test at treatment baseline and as clinically indicated for people who are severely ill, clinically unstable or have advanced HIV disease. A person receiving ART is considered clinically stable based on the following criteria: receiving ART for at least six months, no current illnesses, good understanding of lifelong adherence and evidence of treatment success within the past six months (such as all viral load measurements <1000 copies/mL).

CD4 cell count testing can be performed using a variety of technologies, including laboratory-based CD4 analysers, point-of-care technologies, and device-free semi-quantitative rapid tests *(22)*. Many countries have one or more of these options already available from previous investments made when CD4 cell count was used to set priorities among people living with HIV initiating ART. It is suggested that countries map their CD4 network and identify the best technologies and potential mix useful for their context, considering testing volume needs, health-care facility distribution and key characteristics of each assay, such as time to obtain

results, throughput and costs.Although same-day point-of-care CD4 cell count testing supported more rapid ART initiation before the "treat all" policy was adopted *(23)*, the clinical benefits of using same-day point-of-care CD4 cell count testing to more rapidly and effectively identify people living with advanced HIV disease has not yet been studied. However, given the high rates of morbidity and mortality observed among people living with advanced HIV disease, more rapidly identifying people with advanced HIV disease and providing the advanced HIV disease package of care are likely to improve outcomes. To support rapid and, ideally, same-day identification, several technologies are available, both with and without devices *(24)*. As with any diagnostic assay, careful consideration should be given to human resource requirements, quality assurance and service and maintenance (if device-based). Lack of same-day availability of CD4 count results should not be a barrier to initiating ART on the same day. In settings with limited or no access to laboratory-based CD4 cell count and available point-of-care CD4, it may be considered acceptable for use in the context of the advanced HIV disease package, noting the limitation that a point-of-care test is unable to differentiate between an individual who has a CD4 cell count of less than 100 cells/mm^3 and a cell count between 100 and 200 cells/mm^3.

5.3 Providing a package of care

To address these leading causes of morbidity and mortality among people with advanced HIV disease, WHO recommends that a package of interventions, including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions, be offered to everyone (all populations and age groups) living with HIV presenting with advanced HIV disease *(1)*.

Recommendation (2017)

A package of interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions should be offered to everyone presenting with advanced HIV disease *(strong recommendation, moderate-certainty evidence).*

Source: *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (26).*

Rationale for this recommendation

The rationale for this recommendation is based on two randomized controlled trials: REMSTART *(25)* and REALITY *(26)*.

REMSTART *(25)* was conducted in the United Republic of Tanzania and Zambia and randomized 1999 ART-naive adults living with HIV with CD4 count <200 cells/mm^3 to either standard care or standard care plus enhanced clinic-based care with serum cryptococcal antigen screening and pre-emptive antifungal treatment for those who tested cryptococcal antigen–positive and additional community support (comprising a weekly home or community visit by trained and paid lay workers who delivered ART, provided adherence support and monitored participants for signs and symptoms of drug toxicity or new symptoms). The intervention group had 28% fewer people dying: mortality was 13% in the intervention group versus 18% in the group receiving standard care.

REALITY *(26)* enrolled 1805 mainly adults living with HIV (72 were 5–17 years old) with CD4 counts <100 cells/mm^3 in Kenya, Malawi, Uganda and Zimbabwe. All underwent screening for active TB at enrolment and then were randomized to the standard of care (co-trimoxazole) according to national guidelines or an enhanced prophylaxis package: 12 weeks of fluconazole (100 mg once daily), 12 weeks of a fixed-dose combination of co-trimoxazole (800 + 160 mg) + isoniazid (300 mg) + pyridoxine (25 mg) as a scored once-daily tablet, five days of 500 mg of azithromycin once daily and a single dose of 400 mg of albendazole. All drugs were started simultaneously, and ART was offered on the same day as the prophylaxis package.

The enhanced prophylaxis package at the time of ART initiation reduced mortality by 27% (from 12.2% to 8.9%) over 24 weeks. Mortality from *Cryptococcus* species declined considerably, from 1.5% to 0.4%, and mortality from unascertained causes (most people died at home) declined from 6.0% to 3.8%. TB incidence was reduced by 28%, cryptococcal disease by 62% and hospitalization by 17% in the enhanced prophylaxis group versus the standard-of-care group. Most of the deaths in this study occurred within the first three weeks, highlighting the value of early prophylaxis for people with advanced disease.

Implementation considerations

Providing a package of essential interventions focuses attention on preventing, diagnosing and treating the most common causes of morbidity and mortality among people with advanced HIV disease. Identifying people with advanced HIV disease who are eligible for elements of a package of care requires CD4 testing. In addition, determining the immune status of people whose treatment is failing according to virological criteria can help in guiding clinical management decisions. See Chapter 4 on the treatment monitoring algorithm.

Attention should also be paid to other important causes of severe illness not covered by the package, especially in regions in which specific comorbidities and coinfections are prevalent. Of note, increased pill burden and side-effects may affect treatment adherence. To support treatment adherence, shorter regimens for TB preventive treatment are recommended *(27)*. Identifying suitable screening tools for use is also an important research gap.

Table 5.1 summarizes the specific components of the package of interventions that should be offered to people presenting with advanced HIV disease. For detailed guidance on using systematic TB screening for people, including screening tools recommended for people living with HIV and diagnostic tools such as lateral flow urine lipoarabinomannan assay (LF-LAM), WHO-approved molecular rapid diagnostics and TB preventive treatment, see the consolidated guidelines and operational handbooks for TB modules 1, 2 and 3 *(27–29)*.

Clinical considerations

The role of presumptive treatment in managing cryptococcal disease and histoplasmosis as well as preventive therapy for TB, *P. jirovecii* pneumonia and bacterial infections should be considered in settings in which access to diagnostic tests is limited and people present with typical or possible signs and symptoms (especially when accompanied by clinical signs indicating severe illness). A seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided. Other clinical conditions, such as body temperature ≥39°C, can also be considered based on local epidemiology and clinical judgement.

People with advanced HIV disease may start both ART and prophylaxis at the same time *(26)*. However, ART initiation should be deferred when clinical symptoms suggest TB meningitis or cryptococcal meningitis to avoid paradoxical worsening of the existing infection which can be life-threatening *(30)*.

Table 5.1 Components of the package of care for people with advanced HIV disease

	Intervention	CD4 cell count	Adults	Adolescents	Children <10 years
Screening and diagnosis	Screening tools for TB disease for adults and adolescents: WHO-recommended four-symptom screen, chest X-ray, C-reactive protein, WHO-recommended molecular rapid diagnostic test for TB, alone or in combination Screening tools for TB disease among children: symptom screening for children living with HIV	Any	Yes	Yes	Yes (symptom screen only)
	WHO-recommended molecular rapid diagnostics as the first test for pulmonary TB diagnosis among those who screen positive for TB and investigations for extrapulmonary TB as applicable; chest X-ray may also be used to support investigations	Any	Yes	Yes	Yes
	LF-LAM to assist TB diagnosis among people with symptoms and signs of TB	≤200 cells/mm^3 (inpatient) ≤100 cells/mm^3 (outpatient) Or any CD4 count with symptoms or if seriously ill	Yes	Yes	Yes
	Cryptococcal antigen screening	Recommended for <100 cells/mm^3 and considered for 200 cells/mm^3	Yes	Yes	No
Prophylaxis and pre-emptive treatment	Co-trimoxazole prophylaxis	<350 cells/mm^3 or clinical stage 3 or 4 Any CD4 count in settings with high prevalence of malaria or severe bacterial infections	Yes	Yes	Yes For criteria, see Chapter 6
	TB preventive treatment[a]	Any	Yes	Yes	Yes
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive people without evidence of meningitis	<100 cells/mm^3	Yes	Yes	Not applicable (screening not advised)

	Intervention	CD4 cell count	Adults	Adolescents	Children <10 years
ART initiation	Rapid ART initiation[b]	Any	Yes	Yes	Yes
	Defer initiation if clinical symptoms suggest meningitis (TB or cryptococcal)	Any	Yes	Yes	Yes
Adapted adherence support	Tailored counselling to ensure optimal adherence to the advanced HIV disease package, including home visits if feasible	<200 cells/mm^3	Yes	Yes	Yes

[a] TB preventive treatment should be provided in accordance with current WHO guidance *(27)*.

[b] People receiving a positive WHO four-symptom screen should initiate ART while being evaluated for TB if clinical signs and symptoms of meningitis are absent.

5.4 Overview of clinical management of cryptococcal disease

Cryptococcal disease is one of the most important opportunistic infections among people living with advanced HIV disease and is a major contributor to mortality *(14,31–33)*. *Cryptococcus neoformans,* the causative agent of cryptococcal disease, is present in the environment worldwide. Exposure occurs through inhalation.

In 2018, WHO published *Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children (34)*.

Early diagnosis and treatment of cryptococcal meningitis is key to reducing mortality from cryptococcal disease. Health-care professionals should have a low threshold for suspecting cryptococcal meningitis among people with advanced HIV disease. Countries should give priority to reliable access to rapid diagnostic cryptococcal antigen assays, preferably lateral flow assays, for use in CSF, serum, plasma or whole blood.

Of importance, immediate ART initiation is not recommended for adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and ART initiation should be deferred 4–6 weeks from the initiation of antifungal treatment.

Box 5.1 summarizes the recommendations, which are all based on evidence reviewed by the Guideline Development Group *(34)*.

Box 5.1 Summary of recommendations (2018)

Diagnosis of cryptococcal meningitis

For adults, adolescents and children living with HIV suspected of having a first episode of cryptococcal meningitis, prompt lumbar puncture with measurement of CSF opening pressure and rapid cryptococcal antigen assay is recommended as the preferred diagnostic approach *(34)*

(strong recommendation, moderate-certainty evidence for adults and adolescents).

The following diagnostic approaches are recommended, according to the context.

Settings with ready access to and no contraindication for lumbar puncture

1. If both access to a cryptococcal antigen assay (either lateral flow assay or latex agglutination assay) and rapid results (less than 24 hours) are available: lumbar puncture with rapid CSF cryptococcal antigen assay is the preferred diagnostic approach *(34)*

(strong recommendation, moderate-certainty evidence for adults and adolescents).

2. If access to a cryptococcal antigen assay is not available and/or rapid results are not available: lumbar puncture with CSF India ink test examination is the preferred diagnostic approach *(34)*

(strong recommendation, moderate-certainty evidence for adults and adolescents).

Settings without immediate access to lumbar puncture or when lumbar puncture is clinically contraindicated such as significant coagulopathy or suspected space-occupying lesion based on focal nervous system signs or recurrent seizures

1. If both access to a cryptococcal antigen assay and rapid results (less than 24 hours) are available: rapid serum, plasma or whole-blood cryptococcal antigen assays are the preferred diagnostic approaches *(34)*

(strong recommendation, moderate-certainty evidence for adults and adolescents).

2. If a cryptococcal antigen assay is not available and/or rapid access to results is not ensured: prompt referral for further investigation and treatment as appropriate *(34)*

(strong recommendation, moderate-certainty evidence for adults and adolescents).

Prevention and screening

Overarching principle

Screening for cryptococcal antigen is the optimal approach for guiding resources in a public health approach and is the preferred approach for identifying infection when managing people aged 10 years or older presenting with advanced HIV disease *(25)*.

Recommendations

Screening for cryptococcal antigen followed by pre-emptive antifungal therapy *(35)*[a] among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease are recommended before initiating or reinitiating ART for adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3 *(36)*

(strong recommendation, moderate-certainty evidence).

This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(36)*

(conditional recommendation, moderate-certainty evidence).

All people living with HIV with a positive cryptococcal antigen result on screening should be carefully evaluated for signs and symptoms of meningitis and undergo a lumbar puncture, if feasible, with CSF examination and India ink or CSF cryptococcal antigen assay to exclude active cryptococcal disease. India ink has low sensitivity, and a negative result on India ink should be confirmed by CSF cryptococcal antigen testing.

When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adults and adolescents living with HIV who have a CD4 count <100 cells/mm^3 *(37)*

(strong recommendation, moderate-certainty evidence).

This may be considered at a higher CD4 cell count threshold of <200 cells/mm^3 *(36)*

(conditional recommendation, moderate-certainty evidence).

[a] The Southern African HIV Clinicians' Society recommends starting ART two weeks after starting fluconazole, and consideration is being given to starting ART immediately if lumbar puncture excludes cryptococcal meningitis among people who test positive for whole-blood cryptococcal antigen.

Treatment

Induction

The following is recommended as the preferred induction regimen.

- For adults, adolescents and children, a short-course (one-week) induction regimen with amphotericin B deoxycholate (1.0 mg/kg per day) and flucytosine (100 mg/kg per day, divided into four doses per day) is the preferred option for treating cryptococcal meningitis among people living with HIV *(38,39)*

  (strong recommendation, moderate-certainty evidence for adults).

The following induction regimens are recommended as alternative options.

- Two weeks of fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents) + flucytosine (100 mg/kg per day, divided into four doses per day) *(39)*

  (strong recommendation, moderate-certainty evidence).

- Two weeks of amphotericin B deoxycholate (1.0 mg/kg per day) + fluconazole (1200 mg daily, 12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) *(39)*

  (strong recommendation, moderate-certainty evidence).

Consolidation

Fluconazole (400–800 mg daily for adults or 6–12 mg/kg per day for children and adolescents up to a maximum of 800 mg daily) is recommended for the consolidation phase (for eight weeks following the induction phase) *(40,41)*

(strong recommendation, low-certainty evidence).

Maintenance (or secondary prophylaxis)

Fluconazole (200 mg daily for adults or 6 mg/kg per day for adolescents and children) is recommended for the maintenance phase *(42–44)*

(strong recommendation, high-certainty evidence).

Using adjunctive systemic corticosteroids in treating cryptococcal meningitis

Routine use of adjunctive corticosteroid therapy during the induction phase is not recommended in treating adults, adolescents and children who have HIV-associated cryptococcal meningitis *(45)*

(strong recommendation, high-certainty evidence for adults and adolescents).

Timing of ART

Immediate ART initiation is not recommended among adults, adolescents and children living with HIV who have cryptococcal meningitis because of the risk of increased mortality and should be deferred 4–6 weeks from the initiation of antifungal treatment *(46–49)*

(strong recommendation, low-certainty evidence for adults).

The *Guidelines on the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children (34)* also set out good practice principles (Table 5.2).

Preventing, monitoring and managing amphotericin B toxicity. For people living with HIV receiving amphotericin B–containing regimens for treating cryptococcal disease, a minimum package of preventing, monitoring and managing toxicity is recommended to minimize the serious types of amphotericin B–related toxicity, especially hypokalaemia, nephrotoxicity and anaemia *(50–53)*.

Monitoring for and managing raised intracranial pressure. Adults, adolescents and children living with HIV with suspected cryptococcal meningitis should have an initial lumbar puncture and an early repeat lumbar puncture (within 3–5 days) with measurement of CSF opening pressure to assess for raised intracranial pressure regardless of the presence of symptoms or signs of raised intracranial pressure *(54,55)*.

Managing raised intracranial pressure. Therapeutic lumbar puncture: relieve pressure by draining a volume sufficient to reduce the CSF pressure to <20 cm or halving the baseline pressure if extremely high; the persistence or recurrence of symptoms or signs of raised intracranial pressure should determine the frequency of repeat therapeutic lumbar puncture. For people with persistent symptoms of intracranial pressure, repeat daily therapeutic lumbar puncture (with measurement of CSF opening pressure where available) and CSF drainage, if required, are recommended until the symptoms resolve or the opening pressure is normal for at least two days *(34)*.

Monitoring treatment response. Clinical response (including resolution or recurrence of fever, headache and symptoms or signs of raised intracranial pressure) should be assessed daily during the initial two weeks of induction therapy. Among people for whom evidence indicates a sustained clinical response, routine follow-up lumbar puncture after completing induction treatment to assess antifungal treatment response (CSF fungal culture and CSF cryptococcal antigen) or serum or plasma cryptococcal antigen is not recommended in low- and middle-income countries *(34)*.

Managing treatment failure. For people who present with cryptococcal meningitis relapse, the following steps are recommended: start or restart induction treatment according to the recommendations for induction treatment; manage raised intracranial pressure with therapeutic lumbar puncture; and provide adapted adherence support. If ART has not already started, initiating ART after 4–6 weeks of optimal antifungal therapy is recommended *(34)*.

Paradoxical cryptococcal immune reconstitution inflammatory syndrome occurs among 10–50% of people with cryptococcal disease initiating ART *(56)* and is associated with high mortality *(57)*. The median time to onset in reported cohort studies is 1–10 months but typically is 3–12 weeks after initiating ART *(56)*.

Raised intracranial pressure is a common feature of cryptococcal immune reconstitution inflammatory syndrome and an important contributor to high mortality *(58)*. Multiple repeat lumbar puncture may be necessary. Optimizing antifungal therapy and reinduction with an amphotericin-based regimen are important if suboptimal antifungal treatment is considered to contribute to developing immune reconstitution inflammatory syndrome *(34)*.

Table 5.2 Scenarios for cryptococcal diagnostic testing

Cryptococcal diagnostic testing scenarios	Preferred clinical approach
Settings with ready access to lumbar puncture and cryptococcal antigen testing	Perform lumbar puncture and rapid cryptococcal antigen testing and obtain results within 24 hours. Initiate treatment for cryptococcal meningitis if positive before starting ART
Settings with ready access to lumbar puncture but no cryptococcal antigen testing	Perform lumbar puncture and cerebrospinal fluid India ink staining, and initiate treatment for cryptococcal disease if positive before starting ART. ART should be delayed 4–6 weeks in accordance with WHO recommendations
Settings with ready access to lumbar puncture but it is clinically contraindicated and cryptococcal antigen testing is available	Perform rapid plasma, serum or whole-blood cryptococcal antigen assay. If the cryptococcal antigen test is positive, initiate pre-emptive antifungal therapy in accordance with WHO recommendations
Settings with ready access to lumbar puncture but it is clinically contraindicated and no cryptococcal antigen testing is available	Immediate referral for further management
No signs and symptoms of meningitis, cryptococcal antigen testing is not available and CD4 count is 100–200 cells/mm^3; or if point-of-care CD4 cell count is <200 cells/mm^3[a]	Start primary fluconazole prophylaxis in accordance with WHO recommendations
No signs and symptoms of meningitis, no cryptococcal antigen testing and no CD4 cell testing available	Clinical assessment and WHO staging to facilitate decision for management, consider referral for further management if unclear

[a] In settings in which a semiquantitative CD4 lateral flow assay is the only tool available to diagnose advanced HIV disease, the application of cryptococcal antigen and TB-LAM screening for everyone screening positive (CD4 <200 cells/mm^3) may be appropriate if alternative testing would imply delays or reduced coverage.

5.5 Overview of clinical management of histoplasmosis

Histoplasmosis is a disease caused by the fungus *Histoplasma capsulatum*; the most frequent clinical presentation among people living with HIV is disseminated histoplasmosis. Symptoms of disseminated histoplasmosis are nonspecific and may be indistinguishable from those of other infectious diseases, especially TB, thus complicating diagnosis and treatment *(59)*. Histoplasmosis is highly endemic in some regions of North America, Central America and South America and is also reported in certain countries of Asia and Africa.

The lack of access to appropriate antifungal therapies and in vitro diagnostics for rapid detection of histoplasmosis and the co-occurrence of other infectious diseases, especially TB, may affect clinical outcomes and underlie the high mortality of disseminated histoplasmosis among people living with HIV *(16,60)*.

Severe or moderately severe histoplasmosis is defined as the presence of at least one sign or symptom involving vital organs: respiratory or circulatory failure, nervous system signs, renal failure, coagulation anomalies and a general alteration of the WHO performance status greater than 2, in which the person is confined to a bed or chair more than half of the waking hours and only capable of limited self-care *(61)*.

In 2020, WHO published *Guidelines on diagnosing and managing disseminated histoplasmosis among people living with HIV (61)*. Box 5.2 summarizes the recommendations, which are all based on evidence reviewed by the Guideline Review Committee *(61)*.

Box 5.2 Summary of recommendations (2020)

Diagnosis of disseminated histoplasmosis among people living with HIV
Among people living with HIV, disseminated histoplasmosis should be diagnosed by detecting circulating *Histoplasma* antigens *(62)* *(conditional recommendation, low-certainty evidence).*
Induction therapy
Treating people living with HIV for severe or moderately severe histoplasmosis: liposomal amphotericin B, 3.0 mg/kg, for two weeks is recommended. In settings in which liposomal amphotericin B is unavailable, deoxycholate amphotericin B, 0.7–1.0 mg/kg, is recommended for two weeks *(63–66)* *(conditional recommendation, very-low-certainty evidence).* As a good practice for people with renal failure, or at risk of renal injury, measures to prevent or treat toxicity are recommended. Induction therapy should be given for two weeks. Since deoxycholate amphotericin B may be associated with renal toxicity, therapy may need to be shorter than two weeks based on the clinical assessment of how the person responds to treatment. Involvement of the central nervous system may require extending induction therapy or increasing dosage. Treating people living with HIV for mild to moderate histoplasmosis: itraconazole 200 mg three times daily for three days and then 200 mg twice daily is recommended *(67,68)* *(conditional recommendation, very-low-certainty evidence).*
Maintenance therapy
Itraconazole 200 mg twice daily for 12 months is recommended *(69–71)* *(conditional recommendation, very-low-certainty evidence).* Less than 12 months of therapy can be considered when the person is clinically stable, receiving ART, has suppressed viral load and the immune status has improved *(72)* *(conditional recommendation, very-low-certainty evidence).*
Timing of ART initiation
ART should be initiated as soon as possible among people with disseminated histoplasmosis for whom central nervous system involvement is not suspected or proven *(48)* *(conditional recommendation, very-low-certainty evidence).*
TB therapy for people coinfected with TB, HIV and histoplasmosis
People living with HIV who also have TB and histoplasmosis coinfection should receive TB therapy according to WHO treatment guidelines *(61)* *(conditional recommendation, very-low-certainty evidence).*

5.6 Advanced HIV disease among children and adolescents

All children younger than five years (who are not already receiving ART and clinically stable) are considered to have advanced disease because evidence shows that 80% of all children initiating ART have severe immunosuppression.

Advanced HIV disease is defined as WHO stage 3 or 4 or a CD4 count <200 cells/mm^3 for children five years or older (the same definition used for adults). All children younger than five years living with HIV are considered as having advanced HIV disease, although those who have been receiving ART for more than one year and are established on ART and older than two years should not be considered to have advanced disease and should be eligible for multimonth dispensing.

Children and adolescents who had previously initiated ART and are re-engaging with care after a period of ART interruption should be assessed for advanced HIV disease and should be offered the advanced HIV disease package as appropriate.

Major causes of morbidity and mortality

The major causes of morbidity and mortality among children living with HIV in low- and middle-income countries are pneumonia (including *P. jirovecii* pneumonia), TB, bloodstream infections, diarrhoeal disease and severe acute malnutrition. No randomized controlled trials have included children to determine the optimal package of care for advanced HIV disease for children. However, the main interventions known to reduce morbidity and mortality among children living with HIV can be summarized as screen, treat, optimize and prevent AIDS (Table 5.1 and Box 5.3).

These recommendations include screening for TB (Table 5.3), severe malnutrition and (for adolescents) cryptococcal meningitis; treatment of TB, severe pneumonia, severe bacterial infections and malnutrition (as well as cryptococcal meningitis); rapid ART unless there are signs of meningitis (as for adults) with appropriate measures to prevent TB disease, pneumococcal disease and other vaccine-preventable diseases. In addition, routine interventions recommended by WHO for children in general such as deworming, malaria prophylaxis, iron and vitamin A supplementation and growth monitoring should all be provided.

Table 5.3 Screening, diagnosis and prevention components of the package of care for children and adolescents with advanced HIV disease

Intervention	Component	<5 years	5–9 years	10–19 years
Screening and diagnosis	Systematic screening for TB at each clinic visit using any one of the symptoms of current cough, fever, weight loss, night sweats or close contact with a person with TB for children younger than 10 years	Yes	Yes	Yes
	Use C-reactive protein for screening for TB disease additionally	No	No	Yes[a]
	Use of chest X-ray for screening for TB disease additionally	May be considered	May be considered	Yes
	WHO-recommended rapid diagnostic test, (induced or expectorated) sputum, gastric aspirate, stool or nasopharyngeal aspirate or other Extrapulmonary specimens (induced or expectorated)	Yes	Yes	Yes
	Inpatients in HIV wards in which the TB prevalence is >10% use WHO-recommended rapid diagnostic tests	No	No	Yes
	LF-LAM assay *(73,74)*	Yes	Yes	Yes
	Cryptococcal antigen screening (specimen: serum, plasma or whole blood) If blood cryptococcal antigen positive or symptomatic, lumbar puncture	No	No	Yes
Prevention, prophylaxis and pre-emptive treatment	Pneumococcal conjugate vaccine (catch-up)	Yes	No	No
	Co-trimoxazole[b]	Yes	Yes	Yes
	TB preventive treatment	Yes	Yes	Yes
	Fluconazole pre-emptive therapy for cryptococcal antigen–positive without evidence of meningitis[c]	Not applicable	Not applicable	Yes

[a] Depending on the resources available, C-reactive protein, chest X-ray or molecular WHO-recommended rapid diagnostic test may be used in addition to the four-symptom screen to enhance TB screening among adolescents.

[b] See text for when to discontinue.

[c] Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive adolescents to prevent the development of invasive cryptococcal disease is recommended before initiating or reinitiating ART for adolescents living with HIV who have a CD4 count <100 cells/mm^3 *(strong recommendation, moderate-certainty evidence)* and may be considered at a higher CD4 count threshold of <200 cells/mm^3 *(conditional recommendation, moderate-certainty evidence)*. When cryptococcal antigen screening is not available, fluconazole primary prophylaxis should be given to adolescents living with HIV who have a CD4 count <100 cells/mm^3 *(strong recommendation, moderate-certainty evidence)* and may be considered at a higher CD4 cell count threshold of<200 cells/mm^3 *(conditional recommendation, moderate-certainty evidence)*. Screening and primary prophylaxis are not recommended for children younger than 10 years, given the low incidence of cryptococcal meningitis in this age group *(34)*.

The main differences in the package of care for children compared with adolescents and adults is that routine cryptococcal antigen screening and pre-emptive therapy are not recommended for children younger than 10 years because of the low prevalence of cryptococcal meningitis in this age group. However, if a child younger than 10 years presents with signs and symptoms of meningitis, cryptococcal meningitis should still be considered and the appropriate investigations and treatment for this should be implemented (Table 5.1).

The burden of TB is still high among children living with HIV. Table 5.1 and Box 5.3 highlight the main recommendations for TB screening. Data on LF-LAM among children is limited and recommendations are largely extrapolated from adults. Treatment for drug-sensitive TB among children comprises a four-drug regimen that includes rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E) to be provided with available child-friendly, fixed-dose combinations in dispersible formulations to decrease the pill burden and facilitate administration for young children. Drug–drug interactions between rifampicin and LPV/r or DTG need to be considered and ART dosing adjusted accordingly.

Although rapid ART initiation within seven days of diagnosis is a priority, especially for children older than five years, children who require hospitalization for severe acute malnutrition, TB meningitis or other illnesses need to be clinically stabilized first. However, initiating ART is encouraged as part of the child's hospital admission, since referral after discharge may lead to loss to follow-up and failure to initiate ART. Among children with signs of or confirmed TB meningitis, the start of ART should be delayed in accordance with existing guidelines. Similarly, ensuring linkage to the facility in which the child will receive ongoing HIV care on discharge is critical.

Prevention of opportunistic infections in advanced HIV disease among children consists mostly of rapid and optimal ART initiation, preventing severe TB disease with BCG and TB preventive treatment (mainly with isoniazid while drug–drug interactions with rifapentine are ruled out), preventing *P. jirovecii* pneumonia with co-trimoxazole prophylaxis and administering age-appropriate vaccinations and catch-up vaccine administration when indicated (Table 5.3 and Box 5.3).

Box 5.3 Screen, Treat, Optimize and Prevent AIDS among children

Screen[a]	
TB	• Screen for TB using available screening tools as indicated[b] • For those who screen positive, use the following diagnostic tests to confirm TB as applicable[c]: – Rapid molecular diagnostic on (induced) sputum, stool, gastric aspirate or nasopharyngeal aspirate or other extrapulmonary samples if relevant – LF-LAM assay[d]
Cryptococcal infection among adolescents	Serum or plasma or blood cryptococcal antigen screening followed by lumbar puncture if positive or symptomatic
Malnutrition	• Weight-for-height • Height-for-age • Mid-upper arm circumference among children 2–5 years old
Treat	
TB, severe pneumonia, severe bacterial infections, cryptococcal meningitis and severe acute malnutrition	In accordance with WHO guidelines
Optimize	
Rapid ART start	Preferably same-day but no later than seven days after diagnosis with optimal regimens[e]
ART counselling	In accordance with WHO guidelines
Prevent	
Bacterial infections and *P. jirovecii* pneumonia	Co-trimoxazole prophylaxis
TB	TB preventive treatment
Cryptococcal meningitis among adolescents	Fluconazole pre-emptive therapy if cryptococcal antigen positive or cryptococcal antigen unavailable
Vaccinations	• Pneumococcal vaccine • Human papillomavirus • Measles • BCG

[a] Screening refers to screening and diagnostics throughout this publication.

[b] For screening algorithms and screening tools, see *WHO consolidated guidelines on tuberculosis: module 1: prevention: tuberculosis preventive treatment (28)* and *WHO operational handbook on tuberculosis: module 1: prevention: tuberculosis preventive treatment (75)*. Screening and diagnosis of TB for adolescents is the same as for adults.

[c] A negative test result does not exclude TB for children living with HIV for whom there is a strong clinical suspicion of TB.

[d] *Package of care for children and adolescents with advanced HIV disease: stop AIDS: technical brief (76)*.

[e] Unless TB or cryptococcal meningitis is diagnosed *(77)*.



Implementation considerations

Aligning recommendations across multiple guidelines is essential. Guidelines relating not only to HIV (for example, TB and HIV guidelines relating to TB preventive treatment) but also to routine child health and development interventions (vitamin A, deworming and the Expanded Programme on Immunization) should align as much as possible to prevent multiple visits to health services.

At the facility level, centres introducing the advanced HIV disease package for children should provide a child-friendly environment and ensure access to child-specific resources such as drug formulations for children, a mid-upper arm circumference tape, stadiometer, appropriate scales and expertise in phlebotomy for children. Health-care providers should be sensitized on child-specific issues such as growth monitoring and other routine child health interventions. Efforts should additionally be put in place to support and equip parents and caregivers to recognize warning signs and be able to reliably administer the prescribed medications Country-specific programmes with advanced HIV disease services specifically for children have been successfully implemented *(76)*.

Research gaps

Multiple research gaps exist in addressing prevention and care for children living with advanced HIV disease. Better tools are needed to screen and diagnose TB among children living with HIV. Better diagnostics, including the need to develop simplified point-of-care diagnostics for pneumonia (including *P. jirovecii* pneumonia) and for cytomegalovirus disease, whether to empirically treat for TB and/or cytomegalovirus disease among children living with HIV who present with severe pneumonia and what the optimal package of prophylactic interventions for children living with HIV younger than five years should be are all example of critical knowledge gaps.

5.7 Supporting decision-making for providing a package of care

The algorithm for providing a package of care for people with advanced HIV disease (Fig. 5.1) helps to support decision-making for providing care for people with advanced HIV disease *(1)*.

Considerations for specific adult groups and populations

Pregnant and breastfeeding women

The package of care for pregnant and breastfeeding women with advanced HIV is the same as for non-pregnant adults. However, more evidence is needed to support the use of shorter TB preventive treatment regimens in this population. In addition, WHO guidelines on antenatal care provide recommendations on nutrition support, disease prevention and managing common physical symptoms and infant feeding support for women who cannot breastfeed *(78)*.

Region-specific comorbidities and coinfections

Consideration should be given to regional differences in comorbidities and coinfections that may require additional prophylactic, diagnostic and therapeutic options not covered by the package.

5.7.1 People re-engaging with care after treatment interruption or treatment failure

People re-engaging with care after treatment interruption with advanced HIV disease should be offered comprehensive clinical assessment. The package should be given to people who are re-engaging with care after a period of ART interruption or when ART fails and they have developed advanced HIV disease, since such people are likely to benefit from the same set of interventions as ART-naive people with advanced HIV disease.

People interrupting treatment on a NNRTI– containing regimen are at risk of drug resistance and may require more intensive virological monitoring, and consideration should be given to restarting ART using a different regimen – whenever possible a DTG-containing regimen – with a goal of re-establishing viral suppression *(79)*.

For people presenting with diagnoses consistent with treatment failure (defined as a new or recurrent clinical event indicating severe immunodeficiency), WHO recommends viral load testing; CD4 cell count testing is no longer recommended for ART monitoring for people receiving ART who are clinically stable where viral load monitoring is available *(77)*; however, CD4 cell count testing should be specifically prompted for people with a viral load exceeding 1000 copies/mL and for everyone whose clinical presentation suggests advanced HIV disease regardless of ART exposure. For people with suspected treatment failure and advanced HIV disease, CD4 cell count and viral load should be carried out in parallel.

People presenting with advanced HIV disease as a result of treatment failure should also benefit from the advanced HIV disease package, and if they are severely ill, an expedited switch to a new regimen should be considered by reducing the time between the first and second viral load tests (1–3 months) and by paying increased attention to ensuring rapid turnaround and action on the results. Where rapid viral load testing is not available, the decision to switch should be assessed according to the individual clinical presentation. Further research is required to demonstrate the impact of providing such a package of interventions to people presenting with treatment failure: for example, before switching to second-line ART.

5.7.2 Vaccination for people with advanced HIV disease

Providing vaccinations to people living with HIV does not accelerate HIV disease progression and is recommended as an important part of the HIV care package. However, people with severe immunosuppression may be at higher risk of complications from some live attenuated vaccines, and the response to other inactivated vaccines may be less effective because of their degree of immunosuppression. Additional doses or revaccination after immune reconstitution on ART may therefore be required. Nineteen of the 26 WHO vaccination position papers *(80)* provide guidance for people living with HIV.

Additional assessments

In addition to CD4 cell count testing or WHO clinical staging and TB and cryptococcal testing, the following additional assessments can be considered.

- ☐ Does the person have signs of being seriously ill? Should this person be admitted to an inpatient facility?
- ☐ Is the person receiving an ART regimen that may be failing (or has the person interrupted ART)? If so, additional diagnostic tests, particularly a rapid viral load test, and immediate adherence counselling may be considered, and ART regimen switch when appropriate.

Taking history and further investigations or presumptive treatment, as appropriate, for other illnesses should be considered, according to the local epidemiology or patient context if both TB and cryptococcal assessments are negative. This may include investigations for severe bacterial infections, cerebral toxoplasmosis, *P. jirovecii* pneumonia, other fungal infections (histoplasmosis and talaromycosis) and cytomegalovirus disease as well as lumbar puncture for those with symptoms or signs of meningitis. Additional assessments to consider include haematology to identify anaemia, liver function to identify high alkaline phosphatase that can prompt the diagnosis of hepatic granulomas, ultrasonography, full lymph node examination to assess for suspected lymphoma, skin examination to look for Kaposi's sarcoma, anal and genital examination to identify severe HPV or anal cancer, examination of parasitic diarrhoea (stool) and neurological or vision examination.

Based on these additional assessments, appropriate and likely rapid treatment of any and all confirmed diagnoses should be considered. If rapid testing of additional potential comorbidities is not possible, consider presumptive treatment, especially if the person is seriously ill.

5.8 Programme considerations

Particular attention should be paid to people with advanced HIV disease who miss a clinic visit after initiating treatment for an opportunistic infection or during the initial months after starting or restarting ART, since they are at risk of high mortality.

Programmes should ensure capacity for actively tracing such people. Ideally, such people should consent to and be linked with a community-based health worker who may visit them at home.

People with advanced HIV disease require closer follow-up during the initial period of receiving ART to monitor the response to ART and to identify signs and symptoms of possible immune reconstitution inflammatory syndrome. The feasibility of the frequency of visits is context specific and may also depend on the person's ability to travel to the clinical site. People missing appointments should also be rapidly traced by phone or through home visits. Where face-to-face contact is not feasible, distance contact through telephone consultation, mHealth, text messaging or other mobile interventions, or visits through a community health worker or home-based caregiver should be considered, with the consent of the client.

The package of care for people with advanced HIV disease should be offered at both hospitals and decentralized primary care clinics according to the clinical status of the person living with HIV (ambulatory or requiring hospital admission), the clinical skills of the health-care workers and access to diagnostics at the facilities. However, to increase access to the package, improving access at peripheral sites through mobile outreach or decentralization should be encouraged and may be enabled by providing point-of-care diagnostic tests at all levels where feasible (CD4 cell count, cryptococcal antigen testing, LF-LAM testing and molecular TB testing) or through expedited sample transport systems, where necessary.

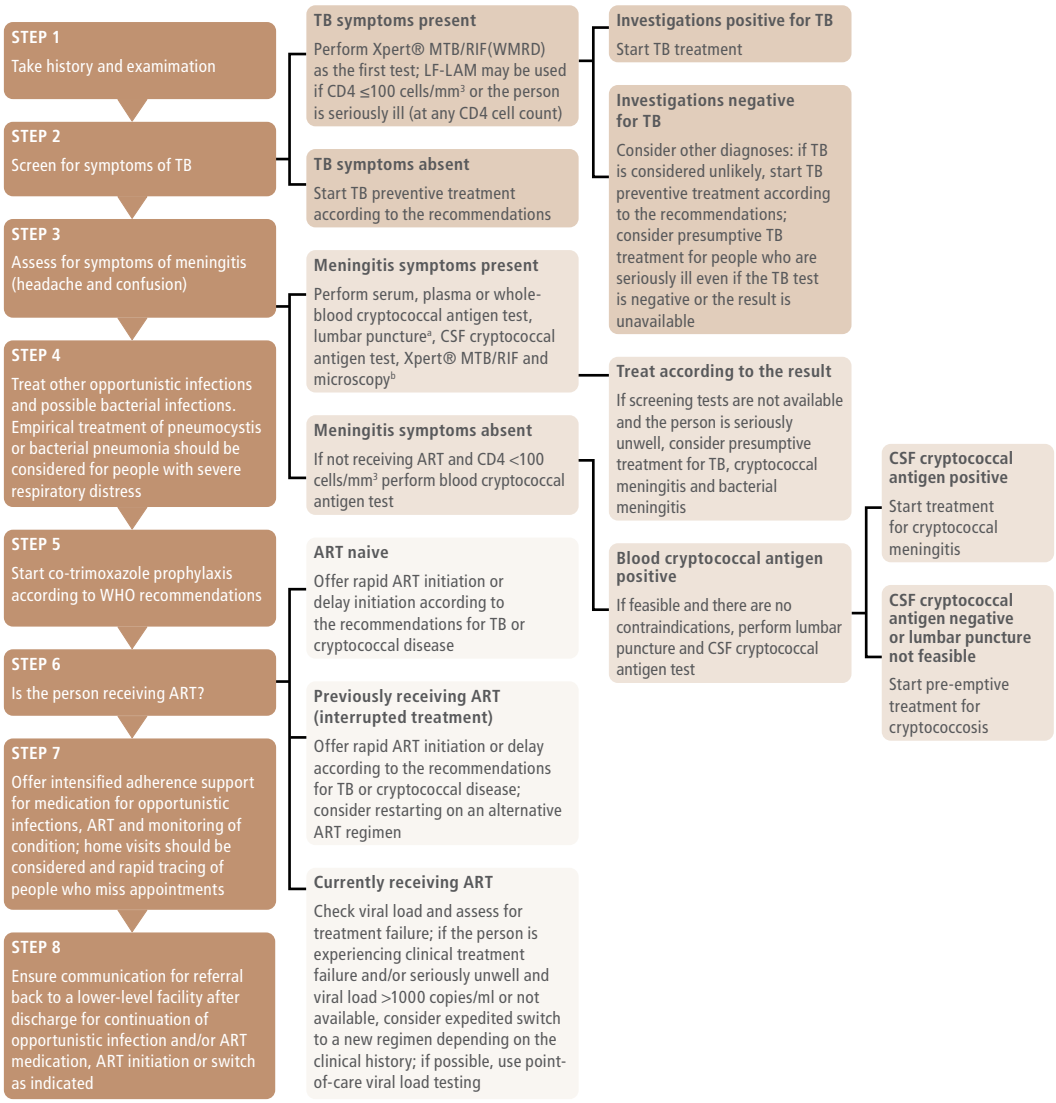
Where care has been decentralized, clear referral criteria should be established to ensure that people requiring further investigation or specialist management receive services in a timely manner. Likewise, referral mechanisms and optimal communication following discharge back to the peripheral clinic must be implemented to ensure appropriate follow-up.

For hospitalized patients, programmes should provide measures to improve linkage and follow-up after discharge such as outpatient primary care clinic visits and home visits by community health workers to reduce the risks of loss to follow-up and of mortality after discharge.

Finally, programmes should provide guidance on reducing the provision of expanded care such as intensified adherence support and home visits for people receiving ART who are clinically stable with CD4 recovery.

Fig. 5.1 Algorithm for providing a package of care for people with advanced HIV disease

- Any person who has signs of being seriously ill should be referred to the appropriate higher-lever facility for management.
- A seriously ill adult is defined as having any of the following danger signs: respiratory rate ≥30 breaths per minute; heart rate ≥120 beats per minute; or unable to walk unaided. Other clinical condition, such as temperature ≥39°C combined with other signs such as headache, can also be considered based on local epidemiology and clinical judgement. A seriously ill child is defined as having any of the following danger signs: lethargy or unconsciousness; convulsions; unable to drink or breastfeed; and repeated vomiting. Other clinical conditions such as temperature ≥39°C and age-defined tachycardia and/or tachypnoea can be considered based on clinical judgement.
- Clear criteria for referral should be available. If the person is not seriously ill, the decision as to what interventions may be decentralized will be programmatic.
- For those hospitalized: mortality is highest in the first 48 hours after admission. Steps 1–4 should be completed as soon as possible on the same day as presentation. Based on clinical assessment: start TB and opportunistic infection therapies as soon as possible among those who are seriously ill. The availability of point-of-care diagnostics (CD4, cryptococcal antigen. LF-LAM and viral load) will support rapid diagnosis, including at decentralized sites.



ART: antiretroviral therapy; CSF: cerebrospinal fluid; TB, tuberculosis; LF-LAM: lateral flow urine lipoarabinomannan assay.

[a] Everyone who is cryptococcal antigen positive and has headache or confusion should have a lumbar puncture.

[b] In settings where test results are available quickly, testing for cryptococcal infection before TB infection would be more cost-effective.

Table 5.4 Recommendations for the package of prophylaxis interventions for people with advanced HIV disease

Intervention	Indication to start			Indication to stop		
	Adults	Adolescents	Children	Adults	Adolescents	Children
Co-trimoxazole prophylaxis	Severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or with a CD4 cell count <350 cells/ mm^3. *Strong recommendation, moderate-certainty evidence* Malaria and/or severe bacterial infections highly prevalent: co-trimoxazole, prophylaxis should be initiated regardless of CD4 cell count or WHO stage. *Conditional recommendation, moderate-certainty evidence*	Same as children	Regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage, those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 count ≤ 350 cells/mm^3. *Strong recommendation, high-certainty evidence*	Clinically stable on ART, with evidence of immune recovery and viral suppression. *Conditional recommendation, low-certainty evidence* Malaria and /or severe bacterial infections are highly prevalent: co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage. *Conditional recommendation, moderate-certainty evidence*	Same as children	High prevalence of malaria and/or severe bacterial infections: continued regardless of whether ART is provided. *Conditional recommendation, moderate-certainty evidence* Low prevalence of malaria and/or severe bacterial infections: discontinued for children who are clinically stable and/ or virally suppressed on ART for at least 6 months and with a CD4 count >350 cells/mm^3. *Strong recommendation, very-low-certainty evidence*

Intervention	Indication to start			Indication to stop		
	Adults	Adolescents	Children	Adults	Adolescents	Children
Pre-emptive antifungal therapy: fluconazole 800 mg/day for two weeks, then 400 mg/day for eight weeks and continued maintenance with fluconazole 200 mg/day	Blood cryptococcal antigen screening positive among people with CD4 counts <100 cells/mm^3 (where lumbar puncture is negative or not feasible or if lumbar puncture excludes cryptococcal meningitis)[a] *Conditional recommendation, low-certainty evidence*	Same as adults	Not applicable since screening is not recommended	If HIV viral load monitoring is not available: when people are stable and adherent to ART and receiving antifungal maintenance therapy for at least one year and have a CD4 count ≥200 cells/mm^3 (two measurements six months apart) *Strong recommendation, low-certainty evidence* If viral load monitoring is available: when people are stable and adherent to ART and antifungal maintenance treatment for at least one year and have a CD4 cell count ≥100 cells/mm^3 (two measurements six months apart) and a suppressed viral load *Conditional recommendation, low-certainty evidence*	Same as adults[b]	Not applicable since screening is not recommended

[a] Everyone with headache or confusion should undergo lumbar puncture.

[b] Dosing of fluconazole for adolescents should be reviewed based on weight.

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GENERAL CARE AND MANAGING COMMON COINFECTIONS AND COMORBIDITIES

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6. GENERAL CARE AND MANAGING COMMON COINFECTIONS AND COMORBIDITIES

6.1 Introduction

ART has reduced mortality and morbidity associated with HIV and transformed HIV into a chronic disease requiring lifetime care. Coinfections and comorbidities, including physical and mental health conditions and substance use disorders, are common among people living with HIV. Comprehensive HIV care includes combination HIV prevention, the promotion of general health and well-being, maintaining quality of life and screening, ART, and the prevention and management of coinfections and comorbidities.

This chapter provides a brief overview of common and important concomitant conditions among people living with HIV. This includes information on co-trimoxazole prophylaxis, the diagnosis, prevention and treatment of TB, viral hepatitis, malaria, sexually transmitted infections, cervical cancer prevention, nutrition, vaccinations, mental health and substance use. It summarizes selected key recommendations, good practice statements and related materials from existing WHO guidelines. Sources are provided for relevant previously published recommendations where more detailed information on their management can be found.

6.2 General care for people living with HIV

Recommendations (2020)

Children and adolescents

Children and adolescents should do at least an average of 60 minutes per day of moderate- to vigorous-intensity, mostly aerobic, physical activity, across the week *(strong recommendation, moderate-certainty evidence)*.

Vigorous-intensity aerobic activities, as well as those that strengthen muscle and bone, should be incorporated at least three days a week *(strong recommendation, moderate-certainty evidence)*.

Children and adolescents should limit the amount of time spent being sedentary, particularly the amount of recreational screen time *(strong recommendation, low-certainty evidence)*.

Adults (18–64 years old) and older adults (65 years and older), including those with chronic conditions

All adults should undertake regular physical activity *(strong recommendation, moderate-certainty evidence)*.

Recommendations (2020) (continued)

Adults should do at least 150–300 minutes of moderate-intensity aerobic physical activity; or at least 75–150 minutes of vigorous intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week, for substantial health benefits *(strong recommendation, moderate-certainty evidence)*.

Adults should also do muscle strengthening activities at moderate or greater intensity that involve all major muscle groups on two or more days a week, since these provide additional health benefits *(strong recommendation, moderate-certainty evidence)*.

Adults may increase moderate-intensity aerobic physical activity to more than 300 minutes; or do more than 150 minutes of vigorous-intensity aerobic physical activity; or an equivalent combination of moderate- and vigorous-intensity activity throughout the week for additional health benefits *(conditional recommendation, moderate-certainty evidence)*.

Adults should limit the amount of time spent being sedentary. Replacing sedentary time with physical activity of any intensity (including light intensity) provides health benefits *(strong recommendation, moderate-certainty evidence)*.

To help reduce the detrimental effects of high levels of sedentary behaviour on health, adults should aim to do more than the recommended levels of moderate- to vigorous-intensity physical activity *(strong recommendation, moderate-certainty evidence)*.

Additional recommendation for older adults (65 years and older)

As part of their weekly physical activity, older adults should do varied multicomponent physical activity that emphasizes functional balance and strength training at moderate or greater intensity, on three or more days a week, to enhance functional capacity and to prevent falls *(strong recommendation, moderate-certainty evidence)*.

Source: *Guidelines on physical activity and sedentary behaviour (1).*

One in four adults and four of five adolescents do not get enough physical activity and 4–5 million deaths per year could be averted if global populations were more physically active *(2)*. WHO has produced evidence-informed guidelines and recommendations on the health effects of physical activity and sedentary behaviour that governments can adopt as part of their national policy frameworks *(1)*. The guidelines provide a cost-effective option that regions, countries or subnational authorities can adapt and use. For adults, physical activity confers benefits for the following health outcomes: reduced all-cause mortality, cardiovascular disease mortality, incident hypertension, incident site-specific cancer,[7] incident type 2 diabetes, improved mental health (reduced symptoms of anxiety and depression), cognitive health and sleep; measures of adiposity may also improve *(1)*.

[7] Site-specific cancers: bladder, breast, colon, endometrial, oesophageal adenocarcinoma, gastric and renal.

Countries should establish a package of general HIV care interventions, in addition to ART, for people living with HIV to reduce HIV transmission, prevent illness and improve their quality of life. General care includes combination HIV prevention, promoting the health of people living with HIV and screening for, prophylaxis for and management of coinfections and comorbidities. WHO has produced summary guidance on general care and prevention interventions *(3–5)* and recommends a package of 13 prevention interventions for adults and adolescents living with HIV in resource-limited settings:

- psychosocial counselling and support;
- disclosure and partner notification;
- co-trimoxazole prophylaxis;
- TB counselling, screening and preventive therapy;
- preventing common fungal infections;
- preventing sexually transmitted infections and supporting reproductive health needs, including preventing and screening for cervical cancer;
- malaria: co-trimoxazole, bed nets and preventing malaria among pregnant women;
- selected vaccine-preventable diseases;
- nutrition;
- family planning;
- prevention of mother-to-child HIV transmission;
- needle and syringe programmes for people who inject drugs; and
- water sanitation and hygiene.

A general care package will vary according to the type of epidemic, populations affected and prevalence of coinfections, other comorbidities and health conditions. Table 6.1 provides an overview of elements of a general care package for people living with HIV. In the era of universal treatment for all people living with HIV, the time between HIV diagnosis, enrolment into care and initiation of ART may be limited to a single visit to reduce loss to follow-up and to provide life-saving ART as soon as possible. WHO no longer recommends the need for preparatory visits before initiating ART; many of the care aspects outlined in Table 6.1 can be accomplished once ART has started *(4,5)*.

Table 6.1 Overview of key elements of general care over the continuum of HIV care for people living with HIV

Service	At HIV diagnosis	At enrolment into care and initiation of ART	Established on ART	At treatment failure and switching ART regimen	At re-engagement following care interruption
General care					
Preparing people for ART	✓	✓			
WHO clinical staging Past and current HIV-related conditions	✓	✓		✓	✓
Preparing, assessing and supporting adherence	✓	✓	✓	✓	✓
Current medications		✓	✓	✓	✓
Pregnancy status Family planning and contraception	✓	✓	✓	✓	✓
Support for disclosure and partner notification	✓	✓			
Risk-reduction counselling and combination HIV prevention approaches	✓	✓	✓	✓	✓
Screening for, preventing and managing noncommunicable diseases		✓	✓	✓	✓
Screening for and managing mental health problems and substance use Psychosocial counselling and support		✓	✓	✓	✓
Managing pain and symptoms		✓	✓	✓	✓
Nutritional assessment and counselling		✓	✓	✓	✓

Table 6.1 Overview of key elements of general care over the continuum of HIV care for people living with HIV (continued)

Service	At HIV diagnosis	At enrolment into care and initiation of ART	Established on ART	At treatment failure and switching ART regimen	At re-engagement following care interruption
Infant and child feeding	✓	✓	✓	✓	✓
Nutritional, growth and development assessment for children and adolescents		✓	✓	✓	✓
Preventing and treating coinfections					
Co-trimoxazole preventive therapy		✓	✓	✓	✓
Intensified TB case-finding		✓	✓	✓	✓
Isoniazid preventive therapy		✓		✓	✓
Screening for cryptococcal infection and fungal prophylaxis when appropriate		✓			✓
Screening for hepatitis B and C		✓		✓	✓
Malaria prevention (insecticide-treated bed nets and prophylaxis)		✓	✓	✓	✓
Screening for sexually transmitted infections		✓	✓	✓	✓
Preventing and screening for cervical cancer		✓	✓	✓	✓
Assessing for vaccine-preventable diseases other than HBV and HCV infection		✓	✓		✓

Research gaps

Despite the large quantity of supporting data relating to physical activity and, increasingly, sedentary behaviour to health outcomes across the lifespan, important evidence gaps remain. There is less evidence from low- and middle-income countries and economically disadvantaged or underserved communities and a dearth of evidence from subpopulations, including people with disabilities. In addition, greater investment is needed in research to build evidence on the precise shape of the dose–response curve between physical activity and/or sedentary behaviour and health outcomes; the health benefits of light-intensity physical activity; and the joint association between physical activity and sedentary behaviour and health outcomes across the life-course.

6.3 Co-trimoxazole prophylaxis

Recommendation (2014)

Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with CD4 cell count ≤350 cells/mm³ *(strong recommendation, moderate-certainty evidence)*.

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage *(conditional recommendation, moderate-certainty evidence)*.

Co-trimoxazole prophylaxis may be discontinued for adults (including pregnant women) with HIV who are clinically stable on ART, with evidence of immune recovery and viral suppression *(conditional recommendation, low-certainty evidence)*.

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage *(conditional recommendation, moderate-certainty evidence)*.

Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, regardless of clinical and immune conditions. Priority should be given to all children younger than five years old regardless of CD4 cell count or clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 cell count ≤350 cells/mm³ *(strong recommendation, high-certainty evidence)*.

In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood whether or not ART is being taken *(conditional recommendation, moderate-certainty evidence)*.

In settings of low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children five years of age and older who are clinically stable and/or virally suppressed on ART for at least six months and CD4 cell count >350 cells/mm³ *(strong recommendation, very-low-certainty evidence)*.

Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from four to six weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding *(strong recommendation, very-low-certainty evidence)*.

Routine co-trimoxazole prophylaxis should be given to all people living with HIV with active TB disease regardless of CD4 cell count *(strong recommendation, high-certainty evidence)*.

Source: *Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children: recommendations for a public health approach – December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (6).*

Background and rationale

Co-trimoxazole is a fixed-dose combination of two antimicrobial agents (sulfamethoxazole and trimethoprim) used to treat a variety of bacterial, fungal and protozoan infections. Co-trimoxazole prophylaxis is a feasible, well-tolerated and inexpensive intervention to reduce HIV-related morbidity and mortality among people living with HIV. Co-trimoxazole is an off-patent drug and is widely available in resource-limited settings.

In 2006, the first WHO guidelines on co-trimoxazole prophylaxis in resource-limited settings recommended co-trimoxazole prophylaxis as an integral component of HIV care *(7)*. These guidelines were reviewed in 2014 and updated in the context of expanded access to and earlier initiation of ART *(6)*. In recent years, new evidence has emerged showing that, with expanded access to ART, co-trimoxazole prophylaxis has broader benefits beyond preventing some AIDS-associated opportunistic diseases (*Pneumocystis jirovecii* pneumonia and toxoplasmosis) and reducing HIV-associated mortality among people with low CD4 cell counts. These benefits relate to preventing malaria and severe bacterial infections among adults and children living with HIV.

Nine observational studies *(8–16)* provide moderate-certainty evidence to support the effectiveness of co-trimoxazole prophylaxis in reducing death among people starting ART with CD4 cell count at or below 350 cells/mm^3 and/or WHO clinical stage 3 or 4 disease. In addition, a new expanded recommendation for using co-trimoxazole prophylaxis is based on a systematic review showing the effectiveness of co-trimoxazole prophylaxis in reducing mortality, severe bacterial infections, malaria and hospitalization among adults and adolescents with HIV regardless of clinical and immunological parameters *(17)*. One randomized clinical trial involving children living with HIV showed survival benefits regardless of age and CD4 cell count and also supports the expansion of co-trimoxazole prophylaxis to children, especially in settings with high prevalence of malaria and/or severe bacterial infections *(18,19)*.

Continuing co-trimoxazole prophylaxis regardless of ART status, age, CD4 cell count or WHO clinical stage in settings with high prevalence of malaria and/or severe bacterial infections is also recommended based on data from randomized controlled trials that show a significant reduction in the risk of hospitalization, malaria and diarrhoea among adults and children with HIV in settings with high prevalence of malaria and/or severe bacterial infections *(20,21)*. In addition, the recommendation to continue co-trimoxazole prophylaxis in settings with a high prevalence of malaria and/or severe bacterial infections may simplify HIV management, forecasting and supply management issues and improve access to co-trimoxazole prophylaxis access for people living with HIV.

The risks and benefits of continuing versus stopping co-trimoxazole prophylaxis after viral suppression induced by ART were also evaluated in settings with a low burden of malaria and severe bacterial infections. Two studies found that the rates of *Pneumocystis jirovecii* pneumonia and death were similar for people receiving ART who achieved suppressed viral loads and had CD4 cell counts above 100 cells/mm^3 in study arms *(22,23)*. In these settings, discontinuing co-trimoxazole prophylaxis for adults based on clinical, immunological and virological parameters indicating ART immune recovery can be considered, although the certainty of the evidence is low to very low *(6)*. However, in settings with a low prevalence of malaria and/or severe bacterial infections and limited or no access to CD4 cell testing, co-trimoxazole prophylaxis should not be discontinued.

The recommendation on women and adolescents living with HIV using co-trimoxazole prophylaxis during pregnancy to prevent malaria complications and avoid simultaneous

intermittent preventive treatment is based on a systematic review showing that co-trimoxazole prophylaxis is not inferior to intermittent preventive treatment of malaria in pregnancy with respect to mortality, low birth weight, placental malaria, maternal deaths and severe adverse events *(24)*. The recommendation to discontinue co-trimoxazole prophylaxis at the end of the risk period for transmission in infants who are HIV-exposed and uninfected is also maintained, but new evidence has emerged on the lack of clinical benefits of co-trimoxazole prophylaxis for HIV-exposed infants who are uninfected and on the potential harm associated with disrupting the microbiome and selecting antibiotic resistance. Where HIV vertical transmission is very uncommon and HIV infection can be reliably excluded, consideration has been given to shorten administration of co-trimoxazole in infants who are HIV exposed but uninfected (see Box 6.1). WHO anticipates reviewing this recommendation as further evidence is gathered and increasing progress is made to rapidly identify infants living with HIV and to retain those exposed to HIV in the testing cascade until final diagnosis is ascertained.

Box 6.1 Using co-trimoxazole among infants who are HIV exposed but uninfected

Since WHO revised the co-trimoxazole guidelines in 2013, new evidence has emerged on the lack of clinical benefits of co-trimoxazole prophylaxis for HIV-exposed infants. A systematic review *(25)* was undertaken to assess the effect of co-trimoxazole prophylaxis on morbidity and mortality among HIV-exposed and uninfected infants. Only two trials from Botswana and South Africa were identified *(26,27)*.

The randomized trial in Botswana (co-trimoxazole $n = 1423$; placebo $n = 1425$) gave co-trimoxazole from 14–34 days until 15 months and showed no evidence of benefit of co-trimoxazole for HIV-exposed and uninfected children for cumulative mortality to 18 months (30 deaths [2.4%] for co-trimoxazole versus 34 deaths [2.6%] for placebo; difference –0.2%, 95% CI –1.5% to 1.0%; primary outcome) or hospitalization, diarrhoea or pneumonia (secondary outcomes; $P > 0.05$). The randomized trial in South Africa (co-trimoxazole $n = 611$; no co-trimoxazole $n = 609$), designed as a non-inferiority trial, gave co-trimoxazole from six weeks until infants were confirmed HIV-uninfected at the end of the at-risk HIV period and showed non-inferiority of not giving co-trimoxazole to HIV-exposed and uninfected children on combined grade 3 and 4 pneumonia, diarrhoea and all-cause mortality by 12 months (primary outcome 49 [8%] events [co-trimoxazole] versus 39 [6%] events [no co-trimoxazole]; risk difference no co-trimoxazole minus co-trimoxazole –0.032, 95% CI –0.075 to 0.011) or pneumonia, diarrhoea and mortality separately ($P > 0.05$). The groups did not differ in anaemia, but one study found that neutropaenia was more frequent in the co-trimoxazole group *(26)*.

Substudies within these trials investigated bacterial resistance and found that the proportion of co-trimoxazole-resistant gastrointestinal bacteria was higher in the co-trimoxazole group *(28)*, and co-trimoxazole prophylaxis decreased gut microbiome β-diversity and increased antibiotic resistance gene α-diversity and prevalence *(29)*. Three further studies examined using co-trimoxazole prophylaxis to prevent malaria *(30–32)*, all in Uganda. These studies found that co-trimoxazole prophylaxis protected against malaria among HIV-exposed and uninfected children when continued after breastfeeding ended, but mortality, hospitalization, diarrhoea and pneumonia were unaffected.

Box 6.1 Using co-trimoxazole among infants who are HIV exposed but uninfected (continued)

To critically review the evidence and explore potential implications for country programmes, WHO convened a technical expert group in March 2021. The group examined current estimates and trends for preventing HIV vertical transmission and coverage of infant testing, noting persisting gaps in timely identification and retention of infants in the testing-to-treatment cascade, with vertical transmission increasingly occurring postnatally. Current co-trimoxazole prophylaxis guidelines provide protection for children at high risk of acquiring HIV who may be missed by infant testing services, but as the systematic review findings suggest, if HIV infection can be reliably excluded, co-trimoxazole does not provide additional benefit to HIV-exposed but uninfected infants and children and may disrupt their microbiomes and increase antibiotic resistance to co-trimoxazole and other widely used antibiotics. This led the South African Thoracic Society to change their guidelines to no longer recommend co-trimoxazole prophylaxis for HIV-exposed and uninfected children (33). However, the studies included in the systematic review were undertaken in Botswana and South Africa, and these findings have limited generalizability to epidemic settings with higher vertical HIV transmission rates, poorer infant testing coverage, higher burden of malaria and other severe bacterial infections and higher infant mortality.

To further explore the potential impact of different approaches across epidemic settings, the group examined the output of a modelling study designed to help quantify the predicted impact of alternative co-trimoxazole strategies on death among HIV-exposed and uninfected children at age two years *(34)*. Assuming full co-trimoxazole uptake, changing current guidelines was predicted to increase mortality in all settings. However, the benefits of the current policy are expected to be greatest in settings with substantial vertical transmission and poor infant testing coverage, in contrast to settings with low vertical transmission and very good infant testing, in which a strategy of shorter co-trimoxazole administration may be a reasonable alternative. This model did not include potential harm associated with disrupting the microbiome and selecting for antibiotic resistance because of the lack of clear clinical correlates.

Current WHO guidelines recommend starting co-trimoxazole for all HIV-exposed infants at age 4–6 weeks and stopping after the period of risk and final confirmation of a negative HIV status, defined as a negative 18-month test or testing after breastfeeding ends if breastfed longer than 18 months. Overall, the expert group thought that the evidence reviewed is compelling, but programme implementation remains challenging in many settings. The group considered fully revising the current recommendations to be premature but the group acknowledged that co-trimoxazole prophylaxis may be discontinued at the end of the at-risk period for HIV transmission (after breastfeeding ends and once HIV infection is ruled out by age-appropriate HIV testing), which may occur before 18 months.

Box 6.1 Using co-trimoxazole among infants who are HIV exposed but uninfected (continued)

Further, in settings with low vertical transmission rates, high HIV infant diagnosis coverage and strong retention in the testing-to-treatment cascade, country programmes may consider stopping providing routine co-trimoxazole as soon as HIV infection is ruled out by age-appropriate HIV testing (see Chapter 2).

Several gaps remain on how to optimize the use of co-trimoxazole prophylaxis among HIV-exposed infants to provide the highest impact. These gaps include optimal timing to start co-trimoxazole; clinical and programmatic impact of shorter duration of co-trimoxazole prophylaxis in different epidemic contexts and programmatic realities; the added value of potential differentiated approaches to co-trimoxazole prophylaxis delivery; the potential impact of shorter co-trimoxazole strategies on retention in the testing-to-treatment cascade; alternative antibiotic prophylactic regimens (other antibiotics); the clinical relevance of the selection of antibiotic resistance associated with co-trimoxazole prophylaxis; and the short- and long-term clinical relevance of the microbiome disruption resulting from co-trimoxazole prophylaxis. Although a randomized blinded clinical trial may not be required to address some of these questions, well-conducted operational research will be critical to innovate and better inform children's use of co-trimoxazole prophylaxis in the future.

Table 6.2 summarizes the criteria for initiating and discontinuing co-trimoxazole prophylaxis for adults, adolescents, pregnant women and children living with HIV.

Table 6.2 Criteria for initiating and discontinuing co-trimoxazole prophylaxis

Population	Recommendations	
	Criteria for initiating co-trimoxazole prophylaxis	Criteria for discontinuing co-trimoxazole prophylaxis
Adults (including pregnant women) living with HIV	• Initiate for everyone with severe or advanced HIV disease (WHO clinical stage 3 or 4) or CD4 cell count ≤350 cells/mm^3 [a] • In settings with high prevalence of malaria and/or severe bacterial infections[b]: initiate for everyone regardless of WHO clinical stage or CD4 cell count	• Stop for those who are clinically stable[c], with evidence of immune recovery and/or suppression of viral loads on ART[d,e] • In settings with high prevalence of malaria and/or severe bacterial infections
Children and adolescents living with HIV	• Initiate for everyone regardless of WHO clinical stage or CD4 cell count • As a priority: – Initiate for everyone younger than five years regardless of WHO clinical stage or CD4 cell count – Initiate for everyone five years and older with severe or advanced HIV disease (WHO clinical stage 3 or 4) or CD4 cell count ≤350 cells/mm^3	• In settings with high prevalence of malaria and/or severe bacterial infections: should not be discontinued until adulthood • In settings with low prevalence of both malaria and severe bacterial infections: may be discontinued for those older than five years who are clinically stable, with evidence of immune recovery[f] and/or suppression of viral loads on ART
HIV-exposed infants	Initiate for everyone starting at 4–6 weeks after birth	Until the risk of HIV transmission ends and HIV infection is excluded with age-appropriate test[g]
People living with HIV and TB[h]	Initiate for everyone with active TB regardless of CD4 cell count	Until the criteria for discontinuation for adults or children are met

[a] This group is also given priority for initiating ART (as recommended for ART in the 2013 WHO consolidated HIV guidelines *(35)*).

[b] Settings where malaria and/or severe bacterial infections are highly prevalent include low- and middle-income countries with high rates of mortality for children younger than five years *(36)*.

[c] Clinically stable adults are defined as individuals receiving ART for at least one year without any new WHO clinical stage 2, 3, or 4 events.

[d] CD4 cell count >350 cells/mm^3, with suppression of viral loads, is considered immune recovery (some countries may adopt a threshold of CD4 cell count >500 cells/mm^3).

[e] WHO recognizes that in settings with low prevalence of malaria and severe bacterial infection in which co-trimoxazole is used primarily as prophylaxis for some AIDS-associated opportunistic infections (*Pneumocystis jirovecii* pneumonia and toxoplasmosis), guidelines exist for adults living with HIV discontinuing co-trimoxazole when there is evidence of suppressed viral loads and immune recovery at CD4 cell count >200 cells/mm^3 and they have been receiving ART for at least one year.

[f] Parameter for immune recovery among children older than five years: CD4 cell count >350 cells/mm^3, with suppressed viral loads.

[g] In settings with low vertical transmission rates, high HIV infant diagnosis coverage and strong retention in the testing-to-treatment cascade, country programmes may consider stopping providing routine co-trimoxazole as soon as HIV infection is ruled out by age-appropriate HIV testing.

[h] Recommendation maintained from *WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders (37)*.

Implementation considerations

Some of the major barriers to implementing co-trimoxazole include supply chain and management issues leading to stock-outs; imposing user charges for medication and/or monitoring; inadequate training, supervision and/or mentoring of health-care workers; low coverage of HIV testing and counselling; and lack of coordination across programmes. National programmes can implement co-trimoxazole prophylaxis policy and guidelines more effectively by using the approaches shown in Box 6.2.

Box 6.2 Steps to improve the implementation of co-trimoxazole prophylaxis policy and guidelines at the national level

- Adapt WHO guidelines to the national context.
- Strengthen national and local drug supply management systems to ensure sustained availability of co-trimoxazole at health-care facilities.
- Secure funding for providing co-trimoxazole prophylaxis to ensure that no user charges are imposed.
- Coordinate with malaria programmes at the country level with regard to recommendations related to intermittent preventive treatment of malaria in pregnancy and seasonal malaria chemoprophylaxis for children younger than five years.
- Provide co-trimoxazole prophylaxis to eligible people at TB, maternal, newborn and child health and opioid substitution therapy services.
- Scale up the training and sensitization of health-care workers.
- Increase co-trimoxazole prophylaxis knowledge at the community level.
- Ensure that a human rights framework is used: for example, people living with HIV should always consent before co-trimoxazole prophylaxis is administered.
- Ensure that high-quality co-trimoxazole formulations are provided.
- Monitor the toxicity of adverse reactions, especially for chronic co-trimoxazole prophylaxis.
- Assess adherence to policies and the impact on population health.

6.4 Tuberculosis

Background

An estimated one fourth of the world's population is infected with TB, and about 5–10% of those infected develop active TB disease in their lifetime. The risk for active TB disease after infection depends on several factors, the most important being the person's immune status *(38)*. People living with HIV are 15–22 times more likely to develop active TB than people without HIV, and TB is the leading cause of death among people living with HIV worldwide *(39,40)*.

WHO has developed and published consolidated guidelines on TB in four modules, designed as living documents that will be updated as new information becomes available:

Module 1: Prevention *(38)*;

Module 2: Screening: systematic screening for tuberculosis disease *(41)*;

Module 3: Diagnosis: rapid diagnostics for tuberculosis detection *(42)*; and

Module 4: Treatment: drug-resistant tuberculosis treatment *(43)*.

Key information from each module is summarized below.

WHO is developing new consolidated guidelines on managing TB among children and adolescents. These guidelines, along with an operational handbook, are expected to be released at the end of 2021; they will consolidate all TB-related recommendations relevant for children (0–9 years old) and adolescents (10–19 years old) in TB, HIV and nutrition guidelines. New evidence will be reviewed on diagnostic approaches (using treatment decision algorithms and using Xpert® Ultra in gastric aspirate and stool specimens), treatment shortening for drug-susceptible TB, treatment of drug-resistant TB, treatment of TB meningitis and models of care (decentralization and family-centred, integrated approaches) among children and adolescents, including those living with HIV.

6.4.1 Screening and diagnosis

Systematic screening for TB among people living with HIV

Recommendation (2021)

People living with HIV should be systematically screened for TB disease at each visit to a health facility *(strong recommendation, very-low-certainty evidence).*

Source: *WHO consolidated guidelines on tuberculosis. Module 2: Screening: systematic screening for tuberculosis disease (41).*

Tools for screening for TB among people living with HIV

Recommendations (2021)

Among adults and adolescents living with HIV, systematic screening for TB disease should be conducted using the WHO-recommended four-symptom screen, and those who report any one of the symptoms of current cough, fever, weight loss or night sweats may have TB and should be evaluated for TB and other diseases *(strong recommendation, moderate-certainty evidence).*

Among children younger than 10 years who are living with HIV, systematic screening for TB disease should be conducted using a symptom screen including any one of the symptoms of current cough, fever, poor weight gain or close contact with a person with TB disease *(strong recommendations, low-certainty evidence for test accuracy).*

Among adults and adolescents living with HIV, C-reactive protein with a cut-off of >5 mg/L may be used to screen for TB disease *(conditional recommendation, low-certainty evidence for test accuracy).*

Among adults and adolescents living with HIV, chest X-ray may be used to screen for TB disease *(conditional recommendation, moderate-certainty evidence for test accuracy).*

Among individuals aged 15 years and older in populations in which TB screening is recommended, computer-aided detection software programmes may be used in place of human readers for interpreting digital chest X-rays for screening and triage for TB disease *(conditional recommendation, low-certainty evidence).*

Among adults and adolescents living with HIV, molecular WHO-recommended rapid diagnostic tests may be used to screen for TB disease *(conditional recommendation, moderate-certainty evidence for test accuracy).*

Adult and adolescent inpatients with HIV in medical wards where the TB prevalence is >10% should be tested systematically for TB disease with a molecular WHO-recommended rapid diagnostic test *(strong recommendation, moderate-certainty evidence for test accuracy).*

Source: *WHO consolidated guidelines on tuberculosis. Module 2: Screening: systematic screening for tuberculosis disease (41).*

Summary of evidence and rationale

In 2019, an estimated 44% of people living with HIV who also had TB disease did not reach care, and TB caused 30% of all HIV-related deaths *(2)*. Thus, ensuring early detection and treatment for TB among all people living with HIV is crucial for reducing morbidity and mortality.

The recommendation to systematically screen for TB disease at each visit to a health facility, which applies to people of all ages, along with the recommendations on related symptom screening algorithms for adults and adolescents and for children, was first published in 2011 in WHO's *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings (19,44)*. For adults and adolescents, the WHO-recommended four-symptom screen is recommended. If an individual screens positive on

any of the following four symptoms: current cough, fever, night sweats and weight loss, they should receive further diagnostic work-up. For children, any of the following symptoms would indicate diagnostic work-up for TB: current cough, fever, poor weight gain or close contact with a person with TB disease.

An individual participant data meta-analysis was conducted in 2020 to review the accuracy of the WHO-recommended four-symptom screen and other tools for TB screening among adults and adolescents, including C-reactive protein, chest X-ray and molecular WHO-recommended rapid diagnostic tests.

WHO four-symptom screen

The meta-analysis of individual patient data found no alternative screening tools or strategies that were significantly higher in both sensitivity and specificity than the WHO-recommended four-symptom screen. In all cases, when sensitivity was higher and met the minimal requirements of the target product profile for a screening test, the specificity was compromised and vice versa. Although the WHO-recommended four-symptom screen may have real-life limitations in terms of consistency and quality of delivery that might not be reflected in studies, it remains the simplest non-invasive tool to implement in any setting, requiring no infrastructure. However, the high proportion of positivity (94%) and very low specificity among medical inpatients living with HIV in settings where the TB prevalence among study participants was >10% gives it limited utility as a screen to rule in TB before diagnostic confirmation by molecular WHO-recommended rapid diagnostic tests in this very ill population. The review also found that the WHO-recommended four-symptom screen had reduced specificity for people not receiving ART (37%, 95% CI 25–59%) and reduced sensitivity for outpatients receiving ART (53%, 95% CI 36–69%). Programmes might therefore want to supplement the WHO-recommended four-symptom screen with other screening tools.

C-reactive protein

The analysis found that C-reactive protein was most accurate among outpatients living with HIV not receiving ART. When performed after a positive WHO-recommended four-symptom screen, C-reactive protein with a cut-off of >5 mg/L was found to be as sensitive as the WHO-recommended four-symptom screen, with a sensitivity of 78% (95% CI 70–85%) but with significantly higher specificity (73%; 95% CI 66–79%) than the WHO-recommended four-symptom screen, which had a sensitivity of 84% (95% CI 75–90%) and specificity of 37% (95% CI 25–50%).

Chest X-ray

The parallel combination of the WHO-recommended four-symptom screen and chest X-ray, in which a positive result from either tool should be followed up by diagnostic confirmation, had the highest sensitivity (85%, 95% CI 69–94%) compared with other tools including the WHO-recommended four-symptom screen (53%, 95% CI 36–69%) when used to screen for TB among outpatients receiving ART.

Computer-aided detection of chest X-ray

Studies comparing the accuracy of computer-aided detection software showed considerable variability among readers, but the substantial overlap of confidence intervals between computer-aided detection software and human readers suggested little difference in accuracy. Limited data were available for comparing computer-aided detection to human interpretation of chest X-ray among people living with HIV; further evidence is needed about the performance of computer-aided detection software among people living with HIV, to enable better setting-specific and patient-specific calibration of computer-aided detection software.

Diagnosing TB

The clinical picture of TB disease is often non-specific and in isolation does not enable its accurate diagnosis, requiring bacteriological testing for all people with signs and symptoms of TB disease. People living with HIV may have an atypical clinical picture, especially those with advanced disease, further complicating the clinical diagnosis of pulmonary and extrapulmonary forms of TB disease.

The diagnostic options recommended by WHO *(42)* are of two broad groups, either initial test for diagnosing TB, often with at least rifampicin resistance detection or those used for follow-on testing after TB confirmation. The latter aimed at detecting additional drug resistance once a TB diagnosis is made and is not covered in this section but covered in the relevant TB guidelines.

Rapid and accurate diagnosis is essential to ensure that people with TB are effectively treated and cured. Table 6.3 shows the initial tests WHO currently recommends. All have recommendations for use among people living with HIV and are considered as WHO rapid diagnostic tests. Furthermore, all are molecular WHO-recommended rapid diagnostic tests except for the lateral flow lipoarabinomannan (LF-LAM) test. Molecular WHO-recommended rapid diagnostic tests are recommended as an initial test rather than smear microscopy or culture, and the diagnostic algorithm 1 provided in the appropriate operational handbook should be followed *(42)*.

LF-LAM is an add-on test specifically for people living with HIV, and the recommendations vary by the presence or absence of symptoms, CD4 cell count and severity of disease requiring hospitalization or not. It is a point-of-care test performed on a urine sample and suited for use as part of the standard package of care for advanced HIV disease. The respective TB guidelines and the accompanying handbook *(42)* provide details. In the latter, algorithms 2a and 2b provide the patient pathways for using LF-LAM for inpatients and outpatients. A positive LF-LAM test predicts mortality, and using the test in advanced HIV accompanied by appropriate and effective treatment saves lives. Next-generation tests with improved sensitivity, including patients with CD4 counts greater than 200 cells/mm^3, have not yet reached commercialization. However, once available and reviewed, these tests offer the potential for broader use within people living with HIV.

Molecular WHO-recommended rapid diagnostic tests are the essential starting-point for diagnosing TB. They include nine different products, with most including simultaneous detection of at least rifampicin resistance. The Xpert® MTB/RIF and Xpert® MTB/RIF Ultra (Xpert® Ultra) have specific recommendations for people living with HIV and extrapulmonary TB. The Xpert® Ultra is more sensitive than the Xpert® MTB/RIF, including for people living with HIV, accompanied by slightly lower specificity. The lower specificity is associated with a previous history of TB treatment in the past five years, mainly when a very low bacterial load is detected, and this semiquantitative result is called "trace". TB DNA may trigger this test result from non-viable organisms among people previously treated, thus being false positive for TB disease.

The Truenat™ and Truenat™ plus tests are suited to similar care levels to the Xpert® and Ultra. Testing for rifampicin is performed as a follow-on reflex test on the same instruments. The TB-LAMP does not test for rifampicin resistance and is thus best suited for areas with a low prevalence of multidrug- and rifampicin-resistant TB. In addition, it requires more hands-on time than other molecular WHO-recommended rapid diagnostic tests. However, it is less expensive both in test costs and equipment than other molecular WHO-recommended rapid diagnostic tests.

The latest addition to the recommended group of molecular WHO-recommended rapid diagnostic tests as initial diagnostic test is the class of moderate complexity automated nucleic acid amplification tests (NAATs). These tests have comparable sensitivity and specificity with other molecular WHO-recommended rapid diagnostic tests in detecting TB and detect resistance to rifampicin and isoniazid. However, this class of tests requires laboratory infrastructure with a rapid and reliable specimen transport system. The class include systems that can perform between 24 and 96 samples in a single run, making it suitable for use in higher-throughput and urban settings. Importantly, this class now includes four new products, all of which have SARS-CoV-2 testing available. Two are widely used for HIV testing and thus facilitate the use of common platforms where capacity exists. The list of products is Abbott RealTi*m*e RealTi*m*e MTB and MTB RIF/INH assays (Abbott Laboratories, Abbott Park, IL, USA), the BD MAX™ multidrug-resistant TB assay (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), the Hain FluoroType® MTBDR assay (Bruker/Hain Lifescience, Nehren, Germany) and the Roche COBAS® MTB and MTB-RIF/INH assays (F. Hoffmann-La Roche, Basel, Switzerland).

All the molecular WHO-recommended rapid diagnostic tests are recommended for diagnosing pulmonary TB. However, for extrapulmonary TB and children, specific recommendations are only provided for Xpert® MTB/RIF, and Xpert® Ultra data for all other tests were limited when the review was conducted. Nevertheless, Xpert® Ultra has higher sensitivity in these groups, and trace positives are considered positive for these populations. Further details on the WHO-recommended diagnostic tools should be consulted in the latest TB consolidated guidelines and operational handbook on diagnostics *(42,45)*.

Molecular WHO-recommended rapid diagnostic tests

Data from the individual participant data analysis found that 94% of medical inpatients had a positive WHO-recommended four-symptom screen, with a specificity of 11%. Thus, the difference in accuracy was minimal between the full screening and diagnostic strategy of using the WHO-recommended four-symptom screen followed by molecular WHO-recommended rapid diagnostic tests and using molecular WHO-recommended rapid diagnostic tests alone. WHO therefore recommends that medical inpatients be screened and tested with a molecular WHO-recommended rapid diagnostic test, regardless of symptoms, to inform a decision about whether to treat for TB. A 10% threshold TB prevalence among hospital inpatients living with HIV is recommended, considering the TB prevalence among the participants studied and striking a balance between ensuring rapid diagnosis in this critically ill population and the need to avoid overtreatment.

Because of the increased sensitivity of molecular WHO-recommended rapid diagnostic tests, but considering the likely challenges relating to access, high costs and feasibility in many countries, molecular WHO-recommended rapid diagnostic tests are also recommended as an option for screening for TB disease among all adults and adolescents living with HIV who are not medical inpatients in settings where the TB prevalence exceeds 10%. In this case, and as with all screening tools, a positive molecular WHO-recommended rapid diagnostic test screen should be followed by a diagnostic assessment to prevent the potential harm of overtreatment. In addition, due consideration should be made to giving priority to molecular WHO-recommended rapid diagnostic tests as a diagnostic test for all people with presumptive TB before scaling up molecular WHO-recommended rapid diagnostic tests as a screening test.

Table 6.3 WHO-recommended rapid diagnostic tests as initial tests for the diagnosis of TB

Diagnostic test[a]	Pulmonary TB sample	Extrapulmonary TB sample	Rifampicin resistance	Isoniazid resistance
Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA)	All adults and children with signs and symptoms Sputum Sputum, gastric aspirate, nasopharyngeal aspirates, stool	Meningitis; cerebrospinal fluid Lymphadenopathy; lymph node aspirate, lymph node biopsy Disseminated TB; blood Other extrapulmonary: Pleural fluid or Peritoneal fluid or Pericardial fluid or Synovial fluid or Urine	Yes	No
Xpert® MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA)	All adults and children with signs and symptoms consistent with TB; includes people living with HIV Sputum Sputum, nasopharyngeal aspirates	Meningitis; cerebrospinal fluid Lymphadenopathy; lymph node aspirate, lymph node biopsy	Yes	No
Truenat™ MTB, MTB Plus and MTB-RIF Dx tests (Molbio Diagnostics, Goa, India)	All adults with signs and symptoms consistent with TB Extrapolated for children Sputum	–	Yes	No
TB-LAMP (Eiken Chemical, Tokyo, Japan)	All adults with signs and symptoms consistent with TB Extrapolated for children Sputum	–	No	No

Table 6.3 WHO-recommended rapid diagnostics tests as initial tests for the diagnosis of TB (continued)

Diagnostic test[a]	Pulmonary TB sample	Extrapulmonary TB sample	Rifampicin resistance	Isoniazid resistance
Moderate complexity automated NAATs **Abbott Laboratories, Abbott Park, USA), the BD MAX™ multidrug-resistant TB assay (Becton, Dickinson and Company, Franklin Lakes, NJ, USA), the Hain FluoroType® MTBDR assay (Bruker/ Hain Lifescience, Nehren, Germany) and the Roche COBAS® MTB and MTB-RIF/INH assays (F. Hoffmann-La Roche, Basel, Switzerland)**	All adults with signs and symptoms consistent with TB Extrapolated for children Sputum	–	Yes	Yes
Urine LF-LAM **Alere Determine™ TB LAM Ag (Chicago, USA)**	People living with HIV only (adults, adolescents and children) with signs and symptoms or advanced HIV disease or low CD4 count Urine	People living with HIV only (adults, adolescents and children) with signs and symptoms or advanced HIV disease or low CD4 count Urine	No	No

[a] The choice of diagnostic test is dependent on the prevailing national policy for TB diagnostics. The key diagnostic tools summarized here are those recommended by WHO.

Source: *WHO consolidated guidelines on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection (45).*

Implementation considerations

Countries should position the WHO-recommended four-symptom screen, C-reactive protein, chest X-ray and molecular WHO-recommended rapid diagnostic tests in combination with diagnostic evaluation using molecular WHO-recommended rapid diagnostic tests and LF-LAM within national TB screening and diagnostic algorithms according to their feasibility, the level of the health facility, resources and equity. Although all the screening tools presented are recommended for all people living with HIV, evidence showed notable accuracy of C-reactive protein for TB screening for people not yet receiving ART and that chest X-ray enhanced the sensitivity of the WHO-recommended four-symptom screen among people receiving ART, both of which might be considered when choosing algorithms. Among inpatients in medical wards in settings with a high TB burden, evidence showed that the WHO-recommended four-symptom screen, C-reactive protein and chest X-ray had limited accuracy because of either extremely low specificity or suboptimal sensitivity and that using molecular WHO-recommended rapid diagnostic tests as an upfront screening and diagnostic test is warranted, particularly given the urgency of timely diagnosis in this population.

Data from the WHIP3TB trial highlight the need to conduct more intensified screening in addition to the WHO-recommended four-symptom screen. Programmes might consider using additional screening tools at the time of initial diagnosis of HIV or during the first antenatal care visit for pregnant women and then annually thereafter. To reduce the burden on the person living with HIV, such screening should be aligned with other routine HIV care visits, such as those for viral load monitoring or for ruling out TB disease before initiating TB preventive treatment, depending on the setting and the national guidelines on HIV. Where applicable, the WHO-recommended four-symptom screen should also be conducted as part of a comprehensive clinical evaluation and to inform the need for increased infection control and for other diagnostic tests, such as LF-LAM. Otherwise screening with the WHO-recommended four-symptom screen alone should be carried out during all other interactions between patients and health-care workers.

Consideration should also be given to the added benefit of including C-reactive protein for ruling out TB disease before initiating TB preventive treatment among people living with HIV. In a setting of 1% TB prevalence, among 1000 outpatients screened with the WHO-recommended four-symptom screen followed by C-reactive protein, 742 would be true negatives and eligible for TB preventive treatment versus only 416 found eligible by the WHO-recommended four-symptom screen. Similar to the case for using chest X-ray for ruling out TB disease before initiating TB preventive treatment, restricted access to C-reactive protein or chest X-ray should not be a barrier to initiating TB preventive treatment. When using a molecular WHO-recommended rapid diagnostic tests as a TB screening tool among people living with HIV is considered, it should be ensured that universal access to molecular WHO-recommended rapid diagnostic tests for everyone with presumptive TB is achieved first. The use of a molecular WHO-recommended rapid diagnostic test as a screening tool requires significant resources for implementation, including increasing the capacity of diagnostic networks and expanding sample transport networks. Depending on the feasibility and resources available, countries may choose to give priority to TB screening using molecular WHO-recommended rapid diagnostic tests among certain subpopulations, such as all medical inpatients, people with advanced disease or pregnant women living with HIV.

To inform programming and resource planning, countries are encouraged to monitor and evaluate the yield of TB screening among people living with HIV, disaggregated by screening tool. Additionally, more data are needed on the effectiveness, cost–effectiveness, feasibility and acceptability, frequency and optimal periodicity of routine, regular screening with the WHO-recommended four-symptom screen, C-reactive protein, chest X-ray and molecular WHO-recommended rapid diagnostic tests among people living with HIV. More studies are needed that explore the optimal placement of molecular WHO-recommended rapid diagnostic tests for screening in antenatal care settings versus within ART clinics. Lastly, more research is needed on the potential for screening people living with HIV with molecular WHO-recommended rapid diagnostic tests using specimens other than sputum.

Extrapulmonary TB among people living with HIV

The risk of extrapulmonary TB is higher among people living with HIV, especially those with lower CD4 cell counts. People living with HIV with extrapulmonary TB often have disseminated disease and are at high risk of rapid clinical deterioration and death. The commonest forms include lymph node (especially in the neck or under the arms), pleural (usually one-sided pleural effusion) and disseminated TB (disease that is not limited to one site in the body). Pericardial and meningeal TB are less frequent forms of extrapulmonary TB but are more likely to result in fatal outcomes *(46)*. The diagnosis of extrapulmonary TB is challenging. Lack of pulmonary findings is not uncommon among people living with HIV with advanced immunosuppression, and disseminated TB can manifest as non-specific febrile illness. Extrapulmonary TB can be suspected among all people living with HIV presenting with TB

symptoms. Further, symptoms suggesting specific organ involvement, such as breathlessness (pleural effusion or pericarditis), enlarged glands in the neck or armpit (lymphadenitis) and chronic headache or altered mental status (meningitis) should prompt further investigation for extrapulmonary TB *(42)*. Bacterial confirmation is often difficult because of low sensitivity of smear microscopy and difficulty in obtaining samples from extrapulmonary sites. If possible, extrapulmonary specimens should be obtained. For people with suspected TB meningitis, a molecular WHO-recommended rapid diagnostic test is the preferred initial diagnostic test for cerebrospinal fluid *(42)*. If lymphadenitis is suspected, molecular WHO-recommended rapid diagnostic tests may be used to test for samples obtained from lymph node biopsies or fine-needle aspiration. LF-LAM may also assist in the diagnosis because these people living with HIV are likely to have low CD4 cell counts *(25)*. The accurate diagnosis of extrapulmonary TB is complex and difficult, especially in peripheral health facilities with limited support and diagnostic infrastructure.

6.4.2 Timing of ART for adults and children with TB

Early initiation of ART among people with both TB and HIV is critical for reducing mortality. Section 4.4.3 provides more detailed information and recommendations on the co-treatment of TB and HIV.

6.4.3 Treatment

Presumptive treatment of TB for people living with HIV

The rationale for presumptive TB treatment, also referred to as empirical treatment, is to prevent the death of people living with HIV in situations when expedited diagnosis of TB is not possible or feasible because of the person's clinical condition or limited access to TB diagnostic services. Although presumptive TB has no case definition, WHO algorithms include initiating TB treatment for people living with HIV in peripheral facilities based exclusively on clinical suspicion (without TB investigations) for seriously ill people[8] based on the judgement of the clinician *(47)*. This approach is based on expert opinion and emphasizes that every effort should be made to confirm the diagnosis of TB after initiating presumptive treatment and that treatment should be stopped only if bacteriological, histological or strong clinical evidence indicates an alternative diagnosis.

In 2015, a systematic review was performed to assess the role of presumptive TB treatment for people living with HIV, with a particular focus on its efficacy in reducing mortality and the risk of severe treatment adverse events. Three randomized controlled trials *(48–50)* were identified.

In the REMEMBER trial, empirical TB therapy did not reduce mortality at 24 weeks among outpatient adults initiating ART with advanced HIV disease. The low mortality rate of the trial supports the implementation of systematic TB screening and intermittent preventive treatment among outpatients with advanced HIV disease *(48)*. In the PrOMPT trial, despite limited enrolment, the study did not suggest that empirical TB treatment among severely immunosuppressed people with low BMI decreased mortality *(49)*. In the STATIS trial, systematic treatment for TB among severely immunosuppressed adults with HIV infection who had not previously received ART was not superior to test-guided treatment in reducing the rate of death or invasive bacterial disease over 24 or 48 weeks and was associated with more grade 3 or 4 adverse events *(50)*.

Based on the available evidence, WHO made no new recommendation on presumptive TB treatment for people living with HIV and noted the importance of further research on this

[8] A person living with HIV is classified as seriously ill if one or more of the following danger signs are present: unable to walk unaided; respiratory rate over 30 per minute; fever of more than 39°C; or pulse rate exceeding 120 per minute.

issue, including research on the clinical predictors for selecting people living with HIV for presumptive treatment and whether nurses or clinical officers can initiate it. Nevertheless, expert opinion continues to support presumptive TB treatment in peripheral health facilities in HIV-prevalent settings for people living with HIV who are seriously ill because of suspected TB.

Implementation considerations

People living with HIV should be closely followed up to assess the occurrence of side-effects related to co-treatment and of TB-associated immune reconstitution inflammatory syndrome, which is common among people with TB starting ART but is usually self-limited *(46)*. Stakeholders and service providers should establish mechanisms to ensure that people living with HIV receive TB treatment along with ART, emphasizing integrated and patient-centred care, preferably at the same location.

Treatment of drug-sensitive TB

Early initiation of ART among people with TB and HIV is critical for reducing mortality. Chapter 4 provides more detailed information and recommendations on the co-treatment of TB and HIV.

At the time of publication, the only current recommended regimen for drug-sensitive TB is a six-month TB regimen containing two months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by four months of rifampicin and isoniazid *(46)*.

However, a recent randomized, multinational, open-label controlled Phase 3 trial, Study 31/A5349, compared the efficacy of a shorter four-month rifapentine-containing regimen comprising rifapentine, isoniazid, pyrazinamide and moxifloxacin with the standard six-month control regimen. As part of the 2020 update of Module 4 of the *WHO consolidated guidelines on tuberculosis*, the data from the trial were reviewed and the efficacy of the four-month rifapentine-based regimen was found to be noninferior to the standard six-month regimen for the treatment of drug-susceptible pulmonary TB and the regimen was equally well tolerated. The available evidence supports using this regimen as a possible alternative to the current standard six-month regimen, including among people living with HIV. The shorter regimen has shown similar performance to the current standard regimen, both in terms of both efficacy and safety. The four-month regimen, which is shorter, effective and all-oral, would be a preference for many people and also national TB and HIV programmes, enabling more rapid cure and easing the burden on both these people and the health-care system. However, implementation and uptake of the new regimen will be more feasible if the cost of rifapentine is reduced and availability improved. It will also require rigorous antibacterial stewardship to ensure the appropriate use of the first-line regimen since it contains moxifloxacin, an antibiotic usually used for drug-resistant TB. Further details, including on eligibility for the shorter treatment regimen for drug-susceptible TB, are available in the 2020 update of Module 4 of the *WHO consolidated guidelines on tuberculosis*.

Significant progress in the availability of improved diagnostics and more effective medicines in recent years have led to earlier detection and higher success rates among people with multidrug- and rifampicin-resistant TB in a number of countries. However, these achievements have not been reproduced globally, and the overall treatment success rate reported in 2018 reached only 56% for people with multidrug- and rifampicin-resistant TB and 39% for people with extensively drug-resistant TB *(51)*. Further information is available in Module 4 of the *WHO consolidated guidelines on tuberculosis*, which replaces all previous and current WHO guidelines on drug-resistant TB treatment *(43)*. Further information, including on drug–drug interactions, is also available in the *WHO operational handbook on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment (52)*.

Treatment of people with drug-resistant TB

Multidrug-resistant TB is TB that is resistant to at least isoniazid and rifampicin. People with both HIV and multidrug-resistant TB face complicated clinical management, fewer treatment options and poorer treatment outcomes *(53)*. Systematic reviews have shown an association between HIV and multidrug-resistant TB *(54,55)*. Outbreaks of multidrug-resistant TB among people living with HIV have been documented in hospital and other settings, especially in eastern Europe and central Asia and in southern African countries with a high HIV prevalence *(56)*.

Recommendation (2020)

WHO recommends ART for all people with HIV and drug-resistant TB, requiring second-line anti-TB drugs irrespective of CD4 cell count, as early as possible (within the first eight weeks) following initiation of anti-TB treatment *(strong recommendation, very-low-certainty evidence).*

Source: *WHO consolidated guidelines on tuberculosis. Module 4: treatment: drug-resistant tuberculosis treatment (43).*

WHO has recently updated guidance on drug-resistant TB, including recommendations on regimens on rifampicin-susceptible isoniazid-resistant TB, a shorter all-oral bedaquiline-containing regimen for multidrug- or rifampicin-resistant TB and longer regimens for multidrug- or rifampicin-resistant TB. There may be a potential for overlapping, additive types of toxicity or for drug–drug interactions between some ARV drugs and the injectable agents moxifloxacin and clofazimine; however, there are usually no grounds to warrant modifying the regimens for multidrug-resistant TB or ART. WHO does not recommend using bedaquiline and efavirenz in combination. ART regimens need to be optimized, and should be initiated early, in accordance with WHO recommendations. Close monitoring for response and toxicity is advised for people receiving both TB and HIV treatment. Other comorbidities (such as diabetes and mental health disorders) should be managed accordingly.

Supporting evidence and rationale

Evidence was reviewed from 10 studies to assess treatment outcomes when ART and second-line anti-TB drugs were used together. None of the data were from randomized controlled trials. Individual data were available for 217 people with drug-resistant TB, of whom 127 received ART. The evidence in individual observational studies varied from low to very low certainty *(43)*.

6.4.4 Prevention

TB preventive treatment

Latent TB is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB disease. An estimated quarter of the world's population is infected with TB.

Among people living with HIV, the combined use of TB preventive treatment and ART has been shown to benefit both TB prevention and mortality, including for people with a higher CD4 cell count *(57–59)*.

Recommendations (2020)

Identifying populations for latent TB infection testing and TB preventive treatment

People living with HIV

- **Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should also be given to those receiving ART, to pregnant women and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if latent TB infection testing is unavailable** *(strong recommendation, high-certainty evidence).*
- **Infants aged <12 months living with HIV who are in contact with a person with TB and who are unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should receive TB preventive treatment** *(strong recommendation, moderate-certainty evidence)*

  Children aged ≥12 months living with HIV who are considered unlikely to have active TB on an appropriate clinical evaluation or according to national guidelines should be offered TB preventive treatment as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with a person with TB *(strong recommendation, low-certainty evidence).*

  All children living with HIV who have successfully completed treatment for TB disease may receive TB preventive treatment *(conditional recommendation, low-certainty evidence).*

For more information on identifying household contacts (regardless of HIV status) for latent TB infection testing and TB preventive treatment: see WHO consolidated guidelines on tuberculosis: Module 1: prevention: tuberculosis preventive treatment (38).

Algorithms to rule out active TB disease

- **Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm. Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered preventive treatment, regardless of their ART status** *(strong recommendation, moderate-certainty evidence).*
- **Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases and offered preventive treatment if active TB is excluded** *(strong recommendation, moderate-certainty evidence).*

  Chest radiography may be offered to people living with HIV receiving ART and TB preventive treatment given to those with no abnormal radiographic findings *(conditional recommendation, low-certainty evidence).*

Recommendations (2020) (continued)

- **Infants and children living with HIV who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should be evaluated for TB and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered TB preventive treatment, regardless of their age** *(strong recommendation, low-certainty evidence).*
- **The absence of any symptoms of TB and the absence of abnormal chest radiographic findings may be used to rule out active TB disease among HIV-negative household contacts aged ≥5 years and other risk groups before TB preventive treatment** *(conditional recommendation, very-low-certainty evidence).*

Testing for latent TB infection

- **Either a tuberculin skin test or interferon-gamma release assay can be used to test for latent TB infection** *(strong recommendation, very-low-certainty evidence).*

TB preventive treatment options

- **The following options are recommended for the treatment of latent TB infection regardless of HIV status: six or nine months of daily isoniazid, or a three-month regimen of weekly rifapentine plus isoniazid, or a three-month regimen of daily isoniazid plus rifampicin** *(strong recommendation, moderate- to high-certainty evidence in the estimates of effect).*
- **A one-month regimen of daily rifapentine plus isoniazid or four months of daily rifampicin alone may also be offered as alternatives** *(conditional recommendation, low- to moderate-certainty evidence).*
- **In settings with high TB transmission, adults and adolescents living with HIV who have an unknown or a positive latent TB infection test and are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy. Daily isoniazid preventive therapy for 36 months should be given whether or not the person is receiving ART and irrespective of the degree of immunosuppression, history of previous TB treatment and pregnancy in settings considered to have high TB transmission as defined by national authorities** *(conditional recommendation, low-certainty evidence).*

Source: *WHO consolidated guidelines on tuberculosis: Module 1: prevention: tuberculosis preventive treatment (38).*

Rationale and evidence

WHO published the recommendation to give TB preventive treatment for all people living with HIV in 2011 *(60)*. A systematic review of 12 randomized controlled trials found that TB preventive treatment reduced the overall risk of TB by 33% (RR 0.67, 95% CI 0.51–0.87) *(61)*.

Pregnancy should not disqualify women living with HIV from receiving preventive treatment with medicines commonly used to treat active TB that are generally considered safe for use in pregnancy, such as isoniazid and rifampicin.

For infants younger than 12 months living with HIV, TB preventive treatment should be given only to those who have a history of household contact with a person with TB and do not have TB disease according to investigations conducted in accordance with national guidelines because of limited data on the benefits *(38)*. TB preventive treatment is strongly recommended for children 12 months or older living with HIV without clinical manifestations suggesting active TB, despite the low certainty of the evidence, because of the clear benefits for adults living with HIV and the high risk of active TB among people living with HIV *(38)*. Children 12 months and older living with HIV who have clinical manifestations or who have contact with a person with TB should be evaluated further and treated for active TB or latent TB infection as indicated. Although the evidence for the efficacy of preventive treatment for children receiving ART is limited, it is biologically plausible given the evidence of additive effects for adults living with HIV receiving ART. Thus, TB preventive treatment is recommended for children living with HIV *(38).*

Implementation considerations

TB preventive treatment for people living with HIV should be a core component of the HIV package of care and should be primarily the responsibility of national HIV and AIDS programmes and HIV service providers *(51)*. In situations where these tests are not available, TB preventive treatment should not be withheld from eligible people if active disease has been excluded on clinical grounds alone, and chest radiography should not be a requirement for initiating preventive treatment.

Ruling out active TB disease

Excluding active TB disease before initiating preventive treatment is one of the critical steps in the latent TB infection care pathway. For adults and adolescents living with HIV, the four-symptom screen – current cough, fever, weight loss and night sweats – is useful for ruling out active TB, regardless of ART use. *WHO consolidated guidelines on tuberculosis: Module 1: prevention: tuberculosis preventive treatment (38)* includes an algorithm for latent TB infection testing and TB preventive treatment for individuals at risk.

TB preventive treatment options

TB preventive treatment for an infection with strains presumed to be drug-susceptible can be broadly categorized into two types: monotherapy with isoniazid for at least six months (isoniazid preventive therapy) and treatment with regimens containing a rifamycin (rifampicin or rifapentine). Isoniazid preventive therapy has been the most widely used type of TB preventive treatment, but the shorter duration of rifamycin regimens presents a clear advantage *(38)*. Preventive treatment for multidrug-resistant TB requires a different regimen using a fluoroquinolone or other second-line agents *(38)*.

WHO has included both recommendations for regimens containing isoniazid or rifamycins in guidance since 2015 *(62)*. Previous WHO guidance included a strong recommendation for TB preventive treatment alternatives to six months of isoniazid monotherapy based on evidence of low to high certainty. In 2019, WHO made two new conditional recommendations for daily rifapentine plus isoniazid for one month and daily rifampicin monotherapy for four months in all settings. These new recommendations are based on low- to moderate-certainty evidence. In addition, instead of a previous range of 3–4 months, WHO now recommends a duration of three months for daily isoniazid plus rifampicin and of four months of daily rifampicin alone to reflect the usual length of time for which these regimens are currently used.

Moreover, three previous recommendations on using six months of isoniazid monotherapy, three months of daily isoniazid plus rifampicin for people younger than 15 years and daily rifapentine plus isoniazid for three months in high-TB-prevalence settings that featured separately in previous guidance are now proposed as alternative options. The revised recommendation makes all latent TB infection options applicable to all settings *(38)*.

Implementation considerations

The recommendation to give at least 36 months of daily isoniazid monotherapy to people living with HIV in high-TB-transmission settings is conditional and based on evidence that longer-term isoniazid preventive therapy significantly adds benefit to ART. The efficacy, safety and convenience of repeated treatment with shorter rifapentine regimens is being studied among people living with HIV in such settings. WHO defines high-TB-transmission settings as those with a high frequency of individuals with undetected or undiagnosed active TB or in which people with infectious TB are present and there is a high risk of TB transmission, but the national authorities should establish the definition. Testing for latent TB infection is not a prerequisite for TB preventive treatment for people living with HIV, but using it is encouraged because people who are positive on a tuberculin skin test have a greater protective benefit from TB preventive treatment. People living with HIV with a negative tuberculin skin test should not receive 36 months of daily isoniazid preventive therapy.

The benefits of three months of daily isoniazid plus rifampicin for infants and children younger than 15 years outweigh the harm, given its safety profile, the higher rate of completion compared with isoniazid monotherapy and the availability of child-friendly, fixed-dose combinations of rifampicin and isoniazid.

All the treatment options can be self-administered. *WHO consolidated guidelines on tuberculosis: Module 1: prevention: tuberculosis preventive treatment (38)* outlines the recommended dosages of medicines for TB preventive treatment.

Drug–drug interactions

Regimens containing rifamycins should be prescribed with caution to people living with HIV who are receiving ART because of potential drug–drug interactions. These regimens should not be administered to people receiving PIs or NVP, including HIV-exposed infants receiving TB preventive treatment. Rifampicin can decrease the concentrations of ATV, DRV, LPV and other PIs. No dose adjustment is required when rifampicin is co-administered with EFV. The dose of DTG needs to be increased to 50 mg twice daily when given together with rifampicin and twice daily dosing should be continued for an additional two weeks following stop of rifampicin use *(63)*. Results from a recent Phase 1/2 trial of daily rifapentine plus isoniazid for three months and DTG for adults living with HIV reported good tolerability and viral load suppression. However, the Guideline Development Group stressed the continued need for studying the pharmacokinetics of daily rifapentine plus isoniazid for three months concomitantly with other medicines, especially ART.

6.4.5 Infection control

The WHO End TB Strategy calls for a 90% reduction in TB deaths and an 80% decrease in the TB incidence rate by 2030. The strategy emphasizes the need for prevention across all approaches, including infection prevention and control in health-care services and other settings with a high risk of *M. tuberculosis* transmission. Infection prevention and control practices are vital to reduce the risk of *M. tuberculosis* transmission, by reducing the concentration of infectious droplet nuclei in the air and the exposure of susceptible individuals to such aerosols.

Details on WHO infection control recommendations are available in the *WHO guidelines on tuberculosis infection prevention and control: 2019 update (64)*.

6.5 Hepatitis B and C

Introduction

Chronic HBV infection (defined as persistence of hepatitis B surface antigen (HBsAg) for more than six months) and chronic HCV infection (defined as HCV antibody–positive with viraemic HCV infection) are major global public health problems *(65,66)*. WHO estimates that, in 2019, 71 million people had chronic HCV infection and 257 million people chronic HBV worldwide, and 820 000 people died from HBV and 290 000 from HCV, mainly from cirrhosis or hepatocellular carcinoma *(67)*. In 2019, there were 1.5 million new chronic HCV infections *(65)*. Transmission of HCV infection has been most commonly associated with unsafe injection or inadequate infection control practices in health-care facilities as well as sharing of needles and syringes among people who inject drugs and transmission among people who inject drugs. HCV viraemic prevalence among people who inject drugs is 39% *(67)*, which accounts for about one third of new HCV infections globally *(68,69)*. There are important differences across countries and regions in the relative contribution of these routes of transmission *(65,66,68)*. The regions with the highest prevalence of chronic HCV infection in the general population (>3.5%) are central and east Asia and North Africa and the Middle East. For HBV infection, perinatal or horizontal transmission is the main route of transmission globally, but transmission also occurs via injecting drug use and high-risk sexual behaviour *(65,66)*. The highest prevalence of HBsAg (>5%) is in sub-Saharan Africa and east Asia, and worldwide, most people with chronic HCB infection were infected at birth or in early childhood, leading to high rates of chronic infection. Between 20% and 30% of those with chronic HBV infection develop complications, mainly cirrhosis and hepatocellular carcinoma. For HCV infection, the risk of cirrhosis ranges from 15% to 30% after 20 years of HCV infection *(70,71)*.

6.5.1 HIV and HBV or HCV coinfection

Globally, the estimated prevalence and burden of HCV coinfection among people living with HIV are 6.2% (interquartile range 3.4–11.9%) and 2.3 million (interquartile range 1.3 million–4.4 million), of which 1.3 million are people who inject drugs. The numbers for HBV coinfection are 7.6% (interquartile range 5.6–12.1%) and 2.7 million (interquartile range 2.0 million–4.2 million) *(71,72)*. Although sub-Saharan Africa has the greatest burden of HIV and HBV coinfection (69% of cases; 1.9 million), for HIV and HCV coinfection, it is in the concentrated epidemic settings of central Asia and eastern Europe among people who inject drugs, which account for 27% of the HIV and HCV burden. HIV and HCV have common routes of transmission, and people living with HIV, especially people who inject drugs *(67)* and gay men and other men who have sex with men *(73)*, have an increased risk of HCV infection. In sub-Saharan Africa, HBV infection is predominantly acquired perinatally or in early childhood. As a result, most people have already been HBV-infected for many years by the time they are exposed to HIV in adulthood *(72)*.

Liver disease caused by coinfection with HBV or HCV is an increasing cause of morbidity and mortality among people living with HIV in some regions, including among people receiving ART. Concurrent infection with HIV usually results in more severe and progressive liver disease and a higher incidence of cirrhosis, hepatocellular carcinoma and mortality *(74,75)*. People living with HIV are therefore a priority group for early diagnosis of viral hepatitis coinfection

and provision of both ART and specific antiviral therapy. In particular, HCV-related liver disease progresses more rapidly among people coinfected with HIV and HCV than among people solely infected with HCV. Even among people for whom ART successfully controls HIV infection (based on undetectable HIV viral load), the risk of hepatic decompensation among coinfected people is higher than among people solely infected with HCV. For these reasons, HCV treatment is a priority for people with HIV and HCV coinfection *(75)*. A comprehensive approach includes prevention, HBV and HCV testing, HBV vaccination and treatment and care for people living with HIV who are coinfected with HBV and/or HCV.

6.5.2 Testing for HBV and HCV infection

Testing and diagnosis of HBV and HCV infection is the gateway for access to both prevention and treatment services. Early identification of people with chronic HBV or HCV infection enables them to receive the necessary care and treatment to prevent or delay the progression of liver disease. Testing also provides an opportunity to link people to interventions to reduce transmission, through counselling on risk behaviour and provision of prevention commodities (such as sterile needles and syringes) and HBV vaccination.

The 2017 testing guidelines recommend offering focused testing to individuals from populations most affected by HBV or HCV infection (either part of a population with higher seroprevalence or have a history of exposure to or high-risk behaviour for HBV or HCV infection) *(70)*. This includes all adults and adolescents living with HIV. For HBV and HCV, other priority groups are mobile and migrant populations from high- and intermediate-endemic countries and certain indigenous populations or those with a history of exposure or high-risk behaviour for HBV infection (such as people who inject drugs; people in prisons and other closed settings; gay men and other men who have sex with men; sex workers; people living with HIV; and the partners, family members and children of people with HBV infection) and health-care workers in all settings. This is in addition to adults, adolescents and children for whom chronic viral hepatitis is clinically suspected (through symptoms, signs or laboratory markers) *(70,76)*.

In settings with a ≥2% or ≥5% seroprevalence of HBsAg or HCV antibody (anti-HCV) (based on existing published thresholds for intermediate or high seroprevalence), it is recommended that all adults have routine access to and be offered testing (a general population testing approach) or use birth cohort testing for specific age groups with higher anti-HCV seroprevalence. In settings with a ≥2% or ≥5%% HBsAg seroprevalence (depending on the epidemic profile and country infrastructure) in the general population, it is recommended that HBsAg serological testing be routinely offered to all pregnant women in antenatal clinics, with linkage to prevention, care and treatment services. Couples and partners in antenatal care settings should also be offered HBV testing services. Overall, these different testing approaches should make use of existing facility-based services (such as outpatient clinics, antenatal clinics, HIV or TB services).

There is also a recent caution on the need to test for HBV infection and consider antiviral therapy before starting direct-acting antiviral therapy among people coinfected with HBV and HCV, because of a potential risk of HBV reactivation and worsening of liver disease. For people living with HIV, ART with a TDF + 3TC or FTC–based regimen should be initiated before starting direct-acting antiviral therapy.

The guidelines recommend using a single quality-assured serological in vitro diagnostic test (either a laboratory-based immunoassay such as enzyme immunoassay or chemiluminescence immunoassay or rapid diagnostic test) to detect HBsAg and HCV antibody. The rapid diagnostic tests used should meet minimum performance standards and be delivered at the point of care to improve access and linkage to care and treatment. Following a reactive HCV antibody serological test result, a quantitative or qualitative RNA NAT is recommended to diagnose viraemic infection. Detecting core HCV antigen, in which the assay has comparable clinical sensitivity to NAT technologies, may be considered as an alternative. The use of HBV DNA NAT following a reactive HBsAg serological test result is recommended to help further guide whom to treat or not treat if no evidence indicates cirrhosis and to monitor for treatment response, based on existing recommendations from the 2015 WHO guidelines on managing HBV *(77)*. There are several WHO-prequalified rapid diagnostic tests for both HCV antibody and HBsAg and one point-of-care HCV RNA viral load NAT assay but not yet for HBV DNA viral load *(78,79)*.

6.5.3 Managing HIV and HCV coinfection

The global response and opportunities for eliminating HCV infection have been transformed by the introduction of curative, short-course direct-acting antiviral therapy, the widespread availability of rapid diagnostic testing for HCV antibody, the availability of NAT for HCV viraemia and the 2018 updated WHO recommendation of a "treat-all" approach regardless of stage of disease using three pangenotypic regimens (see Box 6.3) *(74)*. This is further supported by a simplified public health approach for HCV testing and treatment and good practice principles of decentralization, integration and task sharing to promote the scale-up of testing and treatment.

In general, clinical stabilization of HIV disease with ART is advisable before starting treatment for HCV, especially for people with advanced immunosuppression (CD4 count below 200 cells/mm^3). HCV treatment outcomes with direct-acting antiviral therapy are comparable for people with HIV and HCV coinfection to those solely infected with HCV *(75)*. Because direct-acting antiviral therapy is safe and effective for people with HIV and HCV, they no longer need to be considered as a special or difficult-to-treat population *(80)*. However, pangenotypic HCV regimens and ART have important drug–drug interactions. Checking for drug–drug interactions between HIV and HCV medications is therefore important.

Box 6.3 Pangenotypic regimens currently available for adults 18 years and older

For adults without cirrhosis, the following pangenotypic regimens can be used:

- sofosbuvir + velpatasvir for 12 weeks
- sofosbuvir + daclatasvir for 12 weeks
- glecaprevir + pibrentasvir for 8 weeks.[a]

For adults with compensated cirrhosis, the following pangenotypic regimens can be used:

- sofosbuvir + velpatasvir for 12 weeks
- glecaprevir + pibrentasvir for 12 weeks[a]
- sofosbuvir + daclatasvir for 24 weeks
- sofosbuvir + daclatasvir for 12 weeks.[b]

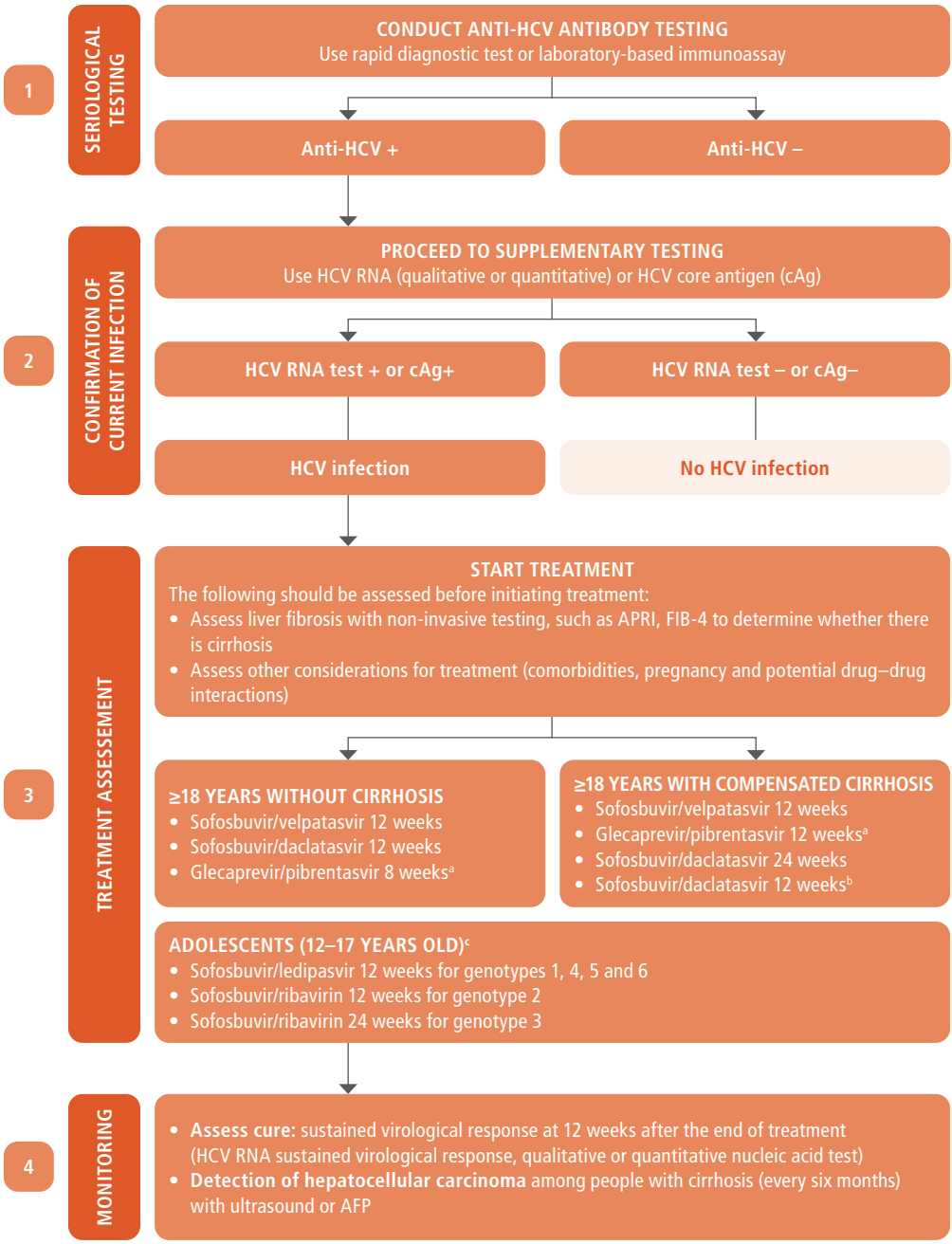
[a] People with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.
[b] May be considered in countries where the genotype distribution is known and the genotype 3 prevalence is <5%.

Pretreatment evaluation

Women of childbearing age may be offered pregnancy testing and be informed about the lack of available data on the safety and efficacy of direct-acting antiviral therapy during pregnancy. In addition, WHO recommends an alcohol intake assessment before initiating treatment and a fibrosis assessment using non-invasive tests such as the AST to platelet ratio index score or FIB-4 test to determine whether there is cirrhosis *(66,74)*. This information will allow clinicians to decide on the appropriate treatment duration of the pangenotypic regimen of their choice based on the absence or presence of cirrhosis. The treatment duration of the recommended pangenotypic regimens sofosbuvir + daclatasvir and glecaprevir + pibrentasvir depends on the absence or presence of cirrhosis (Box 6.3 and Fig. 5.1).

The association between recommended pangenotypic regimens and EFV is either contraindicated (for sofosbuvir + velpatasvir and glecaprevir + pibrentasvir) or requires dose adjustment (for sofosbuvir + daclatasvir). Chapter 4 includes a summary of the drug–drug interactions between WHO-recommended HIV ARV drugs and HCV drugs as do the annexes. Where drug–drug interactions are likely, ARV drug substitutions may be considered before initiating HCV therapy. Prescribers may consult the University of Liverpool webpage on hepatitis drug interactions *(81)* before prescribing, since the details of interactions are frequently updated. This website includes details of interactions with prescribed and non-prescribed medicines.

Fig. 6.1 Algorithm for the diagnosis, treatment and monitoring of chronic HCV infection among adults and adolescents



[a] People with HCV genotype 3 infection who have received interferon and/or ribavirin in the past should be treated for 16 weeks.

[b] May be considered in countries where genotype distribution is known and the genotype 3 prevalence is <5%.

[c] Treating adolescents at this time still requires genotyping to identify the appropriate regimen.AFP: alpha fetoprotein; APRI: aspartate-to-platelet ratio index; FIB-4: fibrosis stage.

6.5.4 Managing HIV and HBV coinfection

HBV vaccination. Universal infant and perinatal HBV vaccination remains the key strategy for preventing mother-to-child transmission and controlling the HBV epidemic. Although high uptake of infant vaccination has been achieved, leading to substantial decreases in incidence in recent years, HBV birth-dose vaccination is being implemented by less than half of countries. The risk of HBV infection may be higher for adults living with HIV, and therefore everyone newly diagnosed with HIV should be screened for HBsAg and anti-HBs to identify those with chronic HCB infection and propose vaccination if non-immune, especially among high-risk groups such as people who inject drugs and gay men and other men who have sex with men. People living with HIV may respond more poorly to HBV vaccine, especially those with a low CD4 cell count. A schedule using four double (40 µg) doses of the vaccine may provide a higher protective anti-HBs titre than the regular three 20 µg dose schedule.

Treatment. In the absence of treatment, HIV coinfection profoundly influences the course of HBV infection, including more rapid progression to cirrhosis and hepatocellular carcinoma, higher liver-related mortality and decreased treatment response compared with people who do not have HIV. All people newly diagnosed with HIV should therefore be screened for HBsAg and vaccinated if HBsAg negative and non-immune (HbsAB <10 IU/L). The recommended NRTI drugs for ART – TDF with 3TC or FTC – are also active against HBV. Fortunately, TDF, a drug widely included in ART regimens, is also the most effective drug for long-term treatment of HBV, leading to sustained HBV viral suppression, reversal of cirrhosis and fibrosis and reduction in HBV-related mortality. WHO guidelines recommend using TDF or entecavir for the long-term treatment of people with chronic HBV infection *(77)*. All people coinfected with HIV and HBV should therefore receive a TDF-based ART regimen in combination with 3TC (or FTC), as the NRTI backbone of an ART regimen, regardless of stage of disease or HBV DNA level. HIV treatment among people coinfected with HBV without using TDF in the regimen may lead rarely to flares of HBV because of ART-associated immune reconstitution. If ARV drugs need to be changed because of HIV drug resistance or toxicity, then TDF with 3TC or FTC should be continued together with the new ARV drugs. Similarly, abrupt treatment discontinuation of TDF or 3TC, may be associated with HBV reactivation, hepatic flares and, in rare cases, hepatic decompensation.

6.5.5 Preventing mother-to-child transmission of HBV infection

Among people living with HIV, HBV coinfection is associated with a higher rate of HBV e-antigen positivity, higher HBV viraemia and increased perinatal transmission of perinatal HBV infection *(13)*. Eliminating HBV infection as a public health threat requires reducing HBsAg prevalence to less than 0.1% among children five years old. This can be achieved by universally immunizing newborns against HBV and other interventions to prevent the mother-to-child transmission of HBV. The 2020 WHO guidelines on antiviral prophylaxis for hepatitis B in pregnancy *(76)* included the following recommendations.

- **Routinely testing pregnant women for HIV, HBV and syphilis.** All pregnant women should be tested for HIV, syphilis and HBsAg at least once and as early as possible in the pregnancy *(HIV standing recommendation since 2007; syphilis: strong recommendation, moderate-certainty evidence; HBsAg: strong recommendation, low-certainty evidence).*
- **Existing recommendations on immunization from the WHO position paper** *(80)***.** All infants should receive their first dose of HBV vaccine as soon as possible after birth, preferably within 24 hours. Delivery of HBV vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose. The birth dose should be followed by two or three doses to complete the primary series.
- **Tenofovir prophylaxis to prevent mother-to-child transmission of HBV.** Women coinfected with HIV and HBV should be receiving TDF-based ART, which will provide prophylaxis to prevent the mother-to-child transmission of HBV. This is in addition to three-dose HBV vaccination for all infants, including timely birth dose *(conditional recommendation, moderate-certainty evidence).*

Table 6.4 Summary of recommendations on testing for chronic HBV and HCV infection

Who to test for chronic HBV infection	
Testing approach and population	**Recommendations[a]**
General population testing	1. In settings with a ≥2% or ≥5%[b] HBsAg seroprevalence in the general population, it is recommended that all adults and adolescents have routine access to and be offered HBsAg serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or health facility–based testing opportunities or programmes such as at antenatal clinics, HIV or TB clinics *(conditional recommendation, low-certainty evidence)*.
Routine testing in pregnant women	2. In settings with a ≥2% or ≥5%[b] HBsAg seroprevalence in the general population, it is recommended that HBsAg serological testing be routinely offered to all pregnant women in antenatal clinics,[c] with linkage to prevention, care and treatment services. Couples and partners in antenatal care settings should be offered HBV testing services *(strong recommendation, low-certainty evidence)*.
Focused testing in most affected populations	3. In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that HBsAg serological testing and linkage to care and treatment services be offered to the following individuals: • **adults and adolescents from populations most affected by HBV infection**[d] (who either are part of a population with high HBV seroprevalence or have a history of exposure and/or high-risk behaviour for HBV infection); • **adults, adolescents and children for whom chronic viral hepatitis**[e] **is clinically suspected** (through symptoms, signs or laboratory markers); • **sexual partners, children and other family members and close household contacts** of those with HBV infection;[f] and • **health-care workers:** in all settings, it is recommended that HBsAg serological testing be offered and HBV vaccination given to all health-care workers who have not been vaccinated previously (adapted from existing guidance on HBV vaccination *(80)*) *(strong recommendation, low-certainty evidence)*.
Blood donors (adapted from existing 2010 WHO guidance (82)	4. In all settings, screening of blood donors should be mandatory with linkage to care, counselling and treatment for those who test positive.

[a] The GRADE system (Grading of Recommendations Assessment, Development and Evaluation) was used to categorize the strength of recommendations as strong or conditional (based on consideration of the certainty of evidence, balance of benefits and harm, acceptability, resource use and programmatic feasibility) and the certainty of evidence as high, moderate, low or very low.

[b] A threshold of ≥2% or ≥5% seroprevalence was based on several published thresholds of intermediate or high seroprevalence. The threshold used will depend on other country considerations and the epidemiological context.

[c] Many countries have chosen to adopt routine testing in all pregnant women, regardless of seroprevalence in the general population, and especially if the seroprevalence ≥2%. A full vaccination schedule including birth dose should be completed for all infants, in accordance with the WHO position paper on HBV vaccines *(80)*.

[d] Includes those who are either part of a population with higher seroprevalence (such as some mobile or migrant populations from high- or intermediate-endemic countries and certain indigenous populations) or have a history of exposure to or high-risk behaviour for HBV infection (such as people who inject drugs; people in prisons and other closed settings; gay men and other men who have sex with men; sex workers; people living with HIV; and partners, family members and children of people with HBV infection).

[e] Features that may indicate underlying chronic HBV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma, or unexplained liver disease, including abnormal liver function tests or liver ultrasound.

[f] In all settings, it is recommended that HBsAg serological testing with HBV vaccination of those who are HBsAg negative and not previously vaccinated be offered to all children with parents or siblings diagnosed with HBV infection or with clinical suspicion of hepatitis, through community- or facility-based testing.

Table 6.4 Summary of recommendations on testing for chronic HBV and HCV infection (continued)

Who to test for chronic HCV infection	
Testing approach and population	**Recommendations[a]**
Focused testing in most affected populations	1. In all settings (and regardless of whether delivered through facility- or community-based testing), it is recommended that serological testing for HCV antibody[b] be offered with linkage to prevention, care and treatment services to the following individuals: • **adults and adolescents from populations most affected by HCV infection**[c] (who are either part of a population with high HCV seroprevalence or have a history of exposure to and/or high-risk behaviour for HCV infection); and • **adults, adolescents and children for whom chronic viral hepatitis is clinically suspected**[d] (through symptoms, signs or laboratory markers) *(strong recommendation, low-certainty evidence)*. *Note:* Periodic retesting using HCV NAT should be considered for those with ongoing risk of acquisition or reinfection.
General population testing	2. In settings with a ≥2% or ≥5%[e] HCV antibody seroprevalence in the general population, it is recommended that all adults have access to and be offered HCV serological testing with linkage to prevention, care and treatment services. General population testing approaches should make use of existing community- or facility-based testing opportunities or programmes such as HIV or TB clinics, drug treatment services and antenatal clinics *(conditional recommendation, low-certainty evidence)*.[f]
Birth cohort testing	3. This approach may be applied to specific identified birth cohorts of older people at higher risk of infectiong and morbidity within populations that have an overall lower general prevalence *(conditional recommendation, low-certainty evidence)*.

[a] The GRADE system (Grading of Recommendations Assessment, Development and Evaluation) was used to categorize the strength of recommendations as strong or conditional (based on consideration of the certainty of evidence, balance of benefits and harm, acceptability, resource use and programmatic feasibility) and the certainty of evidence as high, moderate, low or very low.

[b] This may include fourth-generation combined antibody or antigen assays.

[c] Includes those who are either part of a population with higher seroprevalence (such as some mobile or migrant populations from high- or intermediate-endemic countries and certain indigenous populations) or have a history of exposure to or high-risk behaviour for HCV infection (such as people who inject drugs; people in prisons and other closed settings; gay men and other men who have sex with men; sex workers; people living with HIV; and the children of mothers with chronic HCV infection, especially if HIV-coinfected).

[d] Features that may indicate underlying chronic HCV infection include clinical evidence of existing liver disease, such as cirrhosis or hepatocellular carcinoma or unexplained liver disease, including abnormal liver function tests or liver ultrasound.

[e] A threshold of ≥2% or ≥5% seroprevalence was based on several published thresholds of intermediate and high seroprevalence. The threshold used will depend on other country considerations and the epidemiological context.

[f] Routine testing of pregnant women for HCV infection is currently not recommended.

[g] Because of historical exposure to unscreened or inadequately screened blood products and/or poor injection safety.

6.6 Malaria

Introduction

Malaria continues to cause high levels of morbidity and mortality. Malaria is preventable and treatable, but according to the latest *World Malaria Report (83)*, there were an estimated 22 000 cases and 409 000 deaths globally in 2019. In 2021, WHO published guidelines for malaria *(84)* as a comprehensive resource for advice on malaria.

There is significant geographical overlap between HIV and malaria. People living with HIV have increased risk of more frequent and higher-density infection, severe malaria and malaria-related death, depending on the malaria transmission intensity of the area.

Key interventions to control malaria include early diagnosis, prompt and effective treatment with artemisinin-based combination therapies and use of insecticide-treated nets and indoor residual insecticide spraying to control the vector mosquitoes. In areas of stable malaria transmission, people living with HIV (as for the general population) should routinely use insecticide-treated bed nets or have access to indoor residual spraying to reduce their exposure to malaria. Intermittent preventive treatment during pregnancy and seasonal malaria chemoprophylaxis are also recommended in areas of high transmission. Treatment or intermittent preventive treatment with sulfadoxine-pyrimethamine should not be given to people living with HIV or HIV-exposed infants who are taking co-trimoxazole prophylaxis. Intermittent preventive treatment of malaria in pregnancy should not be provided in addition to co-trimoxazole prophylaxis.

People living with HIV who develop malaria should receive prompt, effective antimalarial treatment regimens. Parasitological confirmation should be undertaken for all suspected malaria cases using either microscopy or a rapid diagnostic test. However, the absence or delay of parasitological diagnosis should not delay the immediate start of antimalarial treatment.

Limited information is available on how HIV infection modifies therapeutic responses to artemisinin-based combination therapies. Early studies suggested that increasing HIV-related immunosuppression was associated with decreased treatment response to antimalarial drugs. There is presently insufficient information to modify the general malaria treatment recommendations for people living with HIV.

Good practice statement (2021)

For people who have HIV and uncomplicated *Plasmodium falciparum* malaria, avoid artesunate + sulfadoxine-pyrimethamine if they are being treated with co-trimoxazole and avoid artesunate + amodiaquine if they are being treated with efavirenz or zidovudine.

Source: *WHO guidelines for malaria (84).*

Supporting evidence and rationale *(84)*

WHO recommends DTG-based regimens as first-line therapy for HIV. In two Phase 2 healthy volunteer studies, participants received 50 mg of DTG once daily alone or in combination with standard treatment doses of artemether + lumefantrine (80/480 mg) or artesunate + amodiaquine (200/540 mg) *(85)*. Co-administration increased DTG clearance by 10.6% (95% CI 4.1–34.5%) and 26.4% (95% CI 14.3–51.4%), respectively. Simulations showed that

simulated trough concentrations of DTG alone or in combination with artemether/lumefantrine or artesunate/amodiaquine are maintained above the DTG protein-adjusted concentration required for 90% inhibition of 0.064 mg/L for more than 99% of the individuals. DTG dose adjustments are not necessary for people taking standard three-day treatment doses of artemether + lumefantrine or artesunate + amodiaquine.

A study of children with uncomplicated malaria in a high-transmission area of Africa showed a decreased risk for recurrent malaria after treatment with artemether + lumefantrine for children receiving LPV/r-based ART versus NNRTI-based ART. Evaluation of pharmacokinetics for these children and for healthy volunteers showed significantly higher exposure to lumefantrine and lower exposure to dihydroartemisinin with LPV/r-based ART but no adverse effects. Conversely, EFV-based ART was associated with a two- to fourfold decrease in exposure to lumefantrine in healthy volunteers and malaria-infected adults and children, with increased rates of recurrent malaria after treatment. Close monitoring is required. Increasing artemether + lumefantrine dosing with EFV-based ART has not yet been studied. Exposure to lumefantrine and other NNRTI-based ART, namely NVP and ETR, did not show consistent changes that would require dose adjustment.

Studies of administration of quinine with LPV/r or RTV alone among healthy volunteers gave conflicting results. The combined data are insufficient to justify dose adjustment. Single-dose atovaquone–proguanil with EFV, LPV/r or ATV/r were all associated with a significantly decreased area under the concentration–time curve for atovaquone (two- to fourfold) and proguanil (twofold), which could well compromise treatment or prophylactic efficacy. There is insufficient evidence to change the current mg/kg body weight dosing recommendations; however, these people should also be monitored closely.

6.7 Buruli ulcer

Introduction

Buruli ulcer, caused by Mycobacterium ulcerans, is largely a health problem among poor people in remote rural areas of sub-Saharan Africa and is the third most common mycobacterial disease after TB and leprosy *(86,87)*. Nearly 50% of the people affected are younger than 15 years, live in remote rural areas and have little or no access to health services *(88)*.

Buruli ulcer and HIV

Areas of sub-Saharan Africa in which Buruli ulcer is endemic also have a high prevalence of HIV, with adult prevalence rates between 1% and 5% *(89)*. Preliminary evidence suggests that HIV infection may increase the risk of Buruli ulcer disease *(90–92)*. Prevalence studies in Benin, Cameroon and Ghana showed that people with Buruli ulcer were 3–8 times more likely to be living with HIV than those without Buruli ulcer *(90,92)*. HIV may affect the clinical presentation of the severity of Buruli ulcer disease, with a reported increased incidence of multiple larger and ulcerated Buruli ulcer lesions among people living with HIV. Buruli ulcer is more common among people living with HIV with low CD4 cell counts, and the size of the Buruli ulcer lesions may increase with decreasing CD4 cell counts *(91–96)*.

Buruli ulcer may occur in the context of immune reconstitution inflammatory syndrome after initiating ART *(97)*.

Diagnosis

In an area of known endemicity, an experienced health-care worker can usually diagnose Buruli ulcer on clinical grounds (86). Molecular detection of *M. ulcerans* by PCR is used to confirm the diagnosis *(89,98)*. If PCR is not available, any of the following or a combination may be used: direct smear examination, PCR, histopathology and culture (not for diagnosis and treatment). For ulcerative lesions, at the start of antibiotic treatment, swabs should be taken from the undermined edges of the ulcer for direct smear examination, culture and PCR. Swabs should also be taken at the end of antibiotic treatment (if the lesion has not healed or surgery is indicated) to enable analysis of the response to treatment. For non-ulcerative lesions, before the start of antibiotic treatment, a fine-needle aspirate should be taken from the estimated centre of the lesion for microbiological analysis (direct smear examination, PCR and culture). Other procedures that can be used to obtain specimens include punch and surgical biopsy if histopathological analysis is strongly required. WHO guidance for obtaining specimens for laboratory confirmation is available *(99)*.

Common differential diagnoses include tropical phagedenic ulcer, necrotizing fasciitis, venous ulcer (especially among older people), diabetic ulcer, sickle-cell disease–related ulcers, yaws, cutaneous TB, leprosy, cutaneous leishmaniasis and malignant skin ulcer *(86)*.

Treatment considerations

The current recommended antibiotic treatment for Buruli ulcer is a combination of rifampicin with clarithromycin or moxifloxacin *(4)*. DTG-based ART is recommended as a preferred first-line regimen for adults, adolescents and children living with HIV who are initiating ART, as recommended for those without Buruli ulcer disease. Because of the pharmacokinetic interaction with rifampicin, it is recommended that the dose of DTG be increased to 50 mg twice daily when both drugs are used concomitantly. The use and management of alternative first-line and second-line regimens should also follow the same principles adopted for people living with HIV without Buruli ulcer disease (see Chapter 4). Clarithromycin and EFV interact to significantly reduce the dose of clarithromycin, potentially reducing its effectiveness and increasing the risk of toxicity (skin rash). Rifampicin and clarithromycin should therefore be used with caution when combined with EFV. The concentrations of most PIs are significantly reduced when combined with rifampicin and should therefore be avoided during antibiotic treatment of Buruli ulcer. If the person is already receiving a PI-based regimen, then the PI should be changed to DTG (with dose adjustment) as the preferred approach *(4)*.

Collaboration with TB programmes at all levels is recommended, especially in areas such as coordinating drug procurement, using laboratory facilities and networks and monitoring for potential antibiotic resistance. Collaboration with HIV and AIDS programmes at all levels is important in managing people with Buruli ulcer, who may be living with HIV. A network of laboratories conducting high-performance PCR-based diagnosis of Buruli ulcer is essential in endemic African countries *(98)*.

Box 6.4 lists the main treatment considerations for Buruli ulcer for people living with HIV.

Box 6.4 HIV and Buruli ulcer coinfection: guiding principles

- Everyone with Buruli ulcer should be offered high-quality facility-based HIV testing and counselling.
- Combination antibiotic treatment for Buruli ulcer should begin before starting ART and given for eight weeks.
- The recommended combination is rifampicin plus clarithromycin. The DTG dose needs to be adjusted because of drug–drug interaction with rifampicin, and this antibiotic regimen should be used with caution when used with ARV drug regimens containing EFV. An alternative antibiotic regimen is rifampicin plus moxifloxacin.
- Rapid ART initiation is recommended for everyone coinfected with Buruli ulcer and HIV, regardless of clinical stage and/or CD4 cell count.
- Everyone coinfected with Buruli ulcer and HIV should be actively screened for TB before beginning Buruli ulcer treatment and before starting ART.
- Everyone coinfected with Buruli ulcer and HIV who has advanced HIV disease should be offered a package of care interventions including screening, treatment and/or prophylaxis for major opportunistic infections, rapid ART initiation and intensified adherence support interventions.
- Programmes should implement a monitoring and reporting system to monitor and evaluate the outcomes of Buruli ulcer and HIV interventions.

Source: *Management of Buruli ulcer–HIV coinfection: technical update (100).*

6.8 Leishmaniasis

Introduction

Leishmaniasis is a group of diseases caused by *Leishmania* species. The three main forms of leishmaniasis are visceral (also known as kala-azar, the most serious form of the disease), cutaneous (the most common) and mucocutaneous *(101)*. Leishmaniasis is caused by the protozoan *Leishmania* parasites, which are transmitted by the bite of infected female phlebotomine sandflies. It is a neglected tropical disease that disproportionately affects poor and marginalized populations with limited access to health care. In 2018, more than 95% of new cases reported to WHO occurred in 10 countries: Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan *(101)*. Although only a small fraction of those infected by *Leishmania* parasites eventually develops the disease, an estimated 700 000 to 1 million new cases occur annually. The burden of visceral leishmaniasis occurring among people living with HIV has increased in recent decades *(102)*.

Leishmaniasis and HIV

Visceral leishmaniasis is an important opportunistic infection associated with HIV infection in some regions *(103)*. The two diseases are mutually reinforcing, with people living with HIV being especially vulnerable to visceral leishmaniasis, and visceral leishmaniasis accelerating HIV replication and disease progression *(103)*. Concomitant HIV infection increases the risk of developing active visceral leishmaniasis by between 100 and 2320 times *(103)*. In areas endemic for visceral leishmaniasis, many people have asymptomatic infection *(104)*. To date, as many as 42 countries throughout the world have reported HIV and leishmaniasis coinfection cases since the first case was reported in 1985 *(105)*. In southern Europe, up to 70% of cases of visceral leishmaniasis among adults are associated with HIV infection *(103)*, although the number of new cases has significantly declined since the end of the 1990s, mainly because of greater access to ART. In parts of the world in which access to ART is limited or leishmaniasis frequently occurs in advanced HIV disease, the prevalence of visceral leishmaniasis coinfection is steadily rising. Northern Ethiopia has a documented high rate of HIV infection among people with visceral leishmaniasis, ranging between 15% and 35% *(106)*. In India, the prevalence of visceral leishmaniasis and HIV coinfection in total reported cases increased from 0.9% in 2000 to 3.8% in 2018. A study from Bihar reported that 5.6% of 2077 consecutive people with confirmed visceral leishmaniasis 14 years and older were living with HIV; half of these were unaware of their HIV status *(107)*.

Clinical presentation of HIV and visceral leishmaniasis coinfection

Visceral leishmaniasis clinical presentations among people living with HIV are frequently atypical and involve various organs (such as the gastrointestinal tract, peritoneal space, lung, pleural space and skin), especially among people with advanced HIV disease and /or low CD4 cell counts. The presence of other concomitant opportunistic infections is common and may make the early clinical diagnosis of visceral leishmaniasis difficult. Cases of visceral leishmaniasis have been described in association with immune reconstitution inflammatory syndrome among people living with HIV with latent *Leishmania* infection or among people already treated for visceral leishmaniasis receiving ART *(103)*.

Diagnosis

Laboratory diagnosis of visceral leishmaniasis is based on positive parasitology (stained smears from bone marrow, spleen, liver, lymph node, blood or culture of the organism from a biopsy or aspirated material) and/or positive serology (indirect fluorescent antibody test, ELISA, rK39 or direct agglutination test) or PCR *(103)*. For visceral leishmaniasis, diagnosis is made by combining clinical signs with parasitological or serological tests (such as rapid diagnostic tests). In cutaneous and mucocutaneous leishmaniasis, serological tests have limited value and clinical manifestation with parasitological tests confirms the diagnosis *(101)*. For people coinfected with HIV and visceral leishmaniasis, diagnostic tests perform less well, with lower sensitivity and specificity of serological tests. For people coinfected with HIV and visceral leishmaniasis, the parasite load is higher, and parasites may be found at unusual sites *(103)*.

Treatment

WHO has guidance on the treatment of people with visceral leishmaniasis and HIV in eastern Africa and South-East Asia *(103)*, recommending liposomal amphotericin B + miltefosine as the preferred treatment regimen to improve treatment efficacy and reduce toxicity. Secondary prophylaxis after the first episode of visceral leishmaniasis is recommended for all people coinfected with HIV and visceral leishmaniasis to reduce the risk of relapse and is summarized in this section. Optimal management of people coinfected with HIV and visceral leishmaniasis aims to cure visceral leishmaniasis and also make HIV viral load undetectable by rapidly initiating ART *(104,108)*.

Pregnancy *(103)*

Little information is available on the treatment of visceral leishmaniasis in pregnancy. The threat of a fatal outcome of leishmaniasis for the mother, the fetus and the newborn is much greater than the risk for adverse drug effects. When untreated, spontaneous abortion, small for birth date and congenital leishmaniasis have been described. In general, amphotericin B deoxycholate and lipid formulations are the best therapeutic options for visceral leishmaniasis. No abortions or vertical transmission have been reported among mothers treated with liposomal amphotericin B. However, the combination regimen to treat visceral leishmaniasis among people coinfected with HIV includes miltefosine, which is potentially embryotoxic and teratogenic and thus should not be used during pregnancy. Experts have recommended to keeping a pregnancy register to evaluate the fetotoxicity of drugs in use.

Implementation considerations

Visceral leishmaniasis diagnostics and medicines need to be continuously available, affordable and accessible to the health systems and to all patients *(109)*. Liposomal amphotericin B and miltefosine are included in the WHO Essential Model List for Medicines *(110)*. Coordination between leishmaniasis and HIV programmes is essential *(111)*.

Recommendations for treating people living with HIV for visceral leishmaniasis (2021)

People coinfected with visceral leishmaniasis and HIV in eastern Africa

Liposomal amphotericin B + miltefosine regimen

Liposomal amphotericin B (up to a total of 30 mg/kg at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for **28 days**)
(conditional recommendation, very-low-certainty evidence).

People coinfected with visceral leishmaniasis and HIV in South-East Asia

Liposomal amphotericin B + miltefosine regimen

Liposomal amphotericin B (up to a total of 30 mg/kg at 5 mg/kg on days 1, 3, 5, 7, 9 and 11) + miltefosine (100 mg/day for **14 days**)
(conditional recommendation, very-low-certainty evidence).

Provide secondary prophylaxis after the first episode of visceral leishmaniasis for all people coinfected with visceral leishmaniasis and HIV.
(conditional recommendation, very-low-certainty evidence).

Key considerations

Routinely screen for TB at visceral leishmaniasis diagnosis and further follow-up.

Consider providing extended therapy for people who do not show good clinical response after ruling out other diagnoses.

When miltefosine is not available, consider using monotherapy with liposomal amphotericin B (up to a total of 40 mg/kg) in accordance with the liposomal amphotericin B regimen.

Provide comprehensive clinical management, including adequate HIV treatment and nutritional support.

Ensure access to contraception and pregnancy testing for women of childbearing age before administering miltefosine.

Source: *WHO guidelines for the treatment of visceral leishmaniasis in HIV-coinfected persons in east Africa and South-East Asia (103).*

6.9 Cervical cancer

Background

Cervical cancer, a preventable and treatable malignancy, is the fourth most commonly detected cancer among women worldwide, with an estimated half million new cases in 2018 *(112)*. More than 311 000 women die from cervical cancer each year, with 87% of these deaths occurring among women living in low- and middle-income countries *(104)*. Although an estimated 5% of all cervical cancer cases are attributable to HIV globally, the proportion of women living with HIV among people with cervical cancer varies widely by region because of the varying prevalence of HIV. In areas with high HIV prevalence, the fraction of cervical cancer attributable to HIV is high and is 40% or more in nine countries versus less than 5% in 122 countries with lower HIV prevalence *(113)*.

Women living with HIV have a six-fold higher risk of cervical cancer than women without HIV *(113)*, and cervical cancer is classified as an AIDS-defining condition *(114)*. This higher risk starts with an increased risk of acquiring HPV infection, lower chances of regression of pre-cancer lesions, more rapid progression to cancer and higher rates of recurrence following treatment *(115–117)*. ART has led to steep declines in AIDS-related mortality and has increased life expectancy, with more than 19 million women estimated to be living with HIV worldwide in 2019 *(118)*.

Following a WHO call to action in 2018, 194 countries collectively resolved to eliminate cervical cancer as a public health problem *(119,120)*. The 2030 targets of the WHO global strategy are to achieve: 90% of girls fully vaccinated with HPV vaccine by age 15 years, 70% of women are screened with a high-performance test by 35 years of age and again by 45 years of age, and 90% of women identified with cervical disease receive treatment.

New recommendations on screening and treatment to prevent cervical cancer

In 2021, WHO published updated guidance on screening and treatment recommendations to prevent cervical cancer *(121)* that included 14 new recommendations and good practice statements for women living with HIV. Table 6.4 summarizes the recommendations for women living with HIV. Screening aims to detect precancerous lesions that can be treated before they progress to cancer. Women living with HIV with access to care have clinical appointments at least every six months, which provides an opportunity for delivering cervical cancer screening and treatment interventions, alongside appropriate follow-up.

WHO guidelines developed in 2021 *(121)* provide recommendations for screening and treatment programmes for cervical cancer prevention.

Supporting evidence

Systematic literature reviews were conducted for the effects of interventions (including tests) on outcomes, and for the accuracy of screening tests in the general population and among women living with HIV. An individual-patient data meta-analysis was performed to analyse age-specific data for cervical cancer and cervical intraepithelial neoplasia among women living with HIV.

A mathematical model, Policy1-Cervix, was also used to estimate the risk of important outcomes of the priority screening and treatment strategies across 78 low- and middle-income countries *(122–124)*. A separate model for cervical cancer among women living with HIV in the United Republic of Tanzania was used to evaluate outcomes for women living with HIV *(125)*. Outcomes were assessed over the lifetime of birth cohorts eligible for screening in 2030 onwards and included cervical cancer incidence and mortality, precancer treatment and additional preterm deliveries as a result of precancer treatment.

Women and girls 15 years and older, regardless of their previous cervical cancer screening or treatment status, were invited to participate in an anonymous, voluntary survey. The survey was promoted through the Union for International Cancer Control and the WHO advisory and advocacy groups for women living with HIV and shared through WHO regional focal points for cervical cancer elimination initiative.

Table 6.5 Summary of WHO screening and treatment recommendations to prevent cervical cancer for women living with HIV

Recommendations for women living with HIV	Strength of recommendation and level of evidence
WHO recommends using HPV DNA detection as the primary screening test rather than visual inspection of the cervix with acetic acid (VIA) or cytology in screening and treatment approaches among women living with HIV. *Remarks:* Existing programmes with quality-assured cytology as the primary screening test should be continued until HPV DNA testing is operational; existing programmes using VIA as the primary screening test should transition rapidly because of the inherent challenges with quality assurance.	*Strong recommendation, moderate-certainty evidence*
WHO suggests using an HPV DNA primary screening test with triage rather than without triage to prevent cervical cancer among women living with HIV.	*Conditional recommendation, moderate-certainty evidence*
In a screen, triage and treat approach using HPV DNA detection as the primary screening test, WHO suggests using partial genotyping, colposcopy, VIA or cytology to triage women living with HIV after a positive HPV DNA test. *Remarks:* The benefits, harm and programmatic costs of the triage options are similar; therefore, the choice of triage method will depend on feasibility, training, programme quality assurance and resources in countries. HPV16/18 genotyping could be integrated into the HPV DNA test.	*Conditional recommendation, moderate-certainty evidence*
When HPV DNA testing is provided, WHO suggests using either samples taken by a health-care provider or self-collected samples.	*Conditional recommendation, low-certainty evidence*
WHO suggests starting regular cervical cancer screening at the age of 25 years among women living with HIV. *Remarks:* Moderate-certainty evidence found that few women living with HIV younger than 25 years are likely to have cervical cancer. This recommendation applies to women living with HIV regardless of when they first tested positive for HIV.	*Conditional recommendation, low-certainty evidence*
After the age of 50 years, WHO suggests that screening be stopped after two consecutive negative screening results, consistent with the recommended regular screening intervals among women living with HIV. Remarks: VIA and ablation treatment are not suitable for screening women for whom the transformation zone is not visible. Inadequate visualization is typical after menopause.	*Conditional recommendation, very-low-certainty evidence*

Table 6.5 Summary of WHO screening and treatment recommendations to prevent cervical cancer for women living with HIV (continued)

Recommendations for women living with HIV	Strength of recommendation and level of evidence
Priority should be given to screening women living with HIV 25–49 years old. When tools are available to manage postmenopausal women, women living with HIV 50–65 years old who have never been screened should also be given priority.	Good-practice statement
WHO suggests a regular screening interval of every 3–5 years when using HPV DNA detection as the primary screening test among women living with HIV.	*Conditional recommendation, low-certainty evidence*
Where HPV DNA testing is not yet operational, WHO suggests a regular screening interval of every three years when using VIA or cytology as the primary screening test among women living with HIV.	*Conditional recommendation, low-certainty evidence*
While transitioning to a programme with a recommended regular screening interval, screening even just twice in a lifetime is beneficial.	Good-practice statement
WHO suggests that women living with HIV who have screened positive on an HPV DNA primary screening test and then negative on a triage test be retested with HPV DNA testing in 12 months and, if negative, move to the recommended screening interval.	*Conditional recommendation, low-certainty evidence*
WHO suggests that women living with HIV who have screened positive on a cytology primary screening test and then have normal results on colposcopy be retested with HPV DNA testing in 12 months and, if negative, move to the recommended regular screening interval.	*Conditional recommendation, low-certainty evidence*
WHO suggests that women living with HIV who have been treated for histologically confirmed CIN2/3 or adenocarcinoma in situ or treated as a result of a positive screening test be retested in 12 months with HPV DNA testing when available rather than with cytology or VIA or co-testing, and, if negative, be retested again at 12 months and, if negative again, move to the recommended screening interval.	*Conditional recommendation, low-certainty evidence*
As programmes introduce HPV DNA testing, use this test when rescreening women living with HIV regardless of the test that was used at the previous screening. In existing programmes with cytology or VIA as the primary screening test, rescreening with the same test should be continued until HPV DNA testing is operational.	Good-practice statement

Source: *Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention: WHO guidelines (126).*

Good practice statement for the general population and women living with HIV

Once a decision to treat a woman is made, treating as soon as possible within six months is good practice to reduce losses to treatment. However, for women who are pregnant, good practice includes deferral until after pregnancy.

In circumstances when treatment is not provided within this time frame, evaluating the woman before treatment is good practice.

Recommendation

WHO suggests large loop excision of the transformation zone or cold-knife conization for women who have histologically confirmed adenocarcinoma in situ.

Remarks: Loop excision may be preferred for women of reproductive age, in settings with greater availability of large loop excision of the transformation zone and by providers with greater expertise performing large loop excision of the transformation zone. Cold-knife conization may be preferred when interpretation of the margins of the histological specimen is imperative. *(Conditional recommendation, low-certainty evidence).*

Source: *Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention: WHO guidelines (126).*

Summary of decision-making, strength and certainty of recommendations

For women living with HIV, a strong recommendation was made for using HPV DNA testing as a primary screening test because a higher value was placed on the reductions in cervical cancer and deaths that are likely with this approach than on the potential harm that may occur, such as preterm deliveries. Compared with VIA or cytology as a primary screening test, greater benefits are also more likely with HPV DNA testing. HPV DNA testing is acceptable to women and providers, is feasible and is not likely to lead to inequities. In some settings, HPV DNA testing is not yet available, however, and existing quality-assured programmes will need to remain until HPV DNA testing becomes operational.

A conditional recommendation was made to use HPV DNA testing with a triage test rather than HPV DNA testing followed by treatment because providing a triage test may lead to reduced potential harm, with minimal change in benefits. The feasibility and resources needed to provide different triage tests vary across settings, thus influencing which test is chosen.

Overall, with all screening and treatment strategies, there are greater reductions in cervical cancer, deaths and CIN2/3 lesions for women living with HIV compared with the general population of women. For women living with HIV receiving ART, there were few data on how ART affects HPV-associated lesions, although the evidence is growing; therefore, recommendations based on using ARV drugs were not made.

For the age at which to start screening, a meta-analysis of individual patient data, mathematical modelling and studies about cervical cancer incidence and cervical intraepithelial neoplasia by age provided low-certainty evidence supporting the initiation of screening at 25 years of age rather than at 20 or 30 years. Starting at this age is likely to be acceptable to stakeholders, is feasible and requires fewer resources than starting screening earlier. The studies mentioned above provided very-low-certainty evidence (given the small numbers of women followed and reporting cervical cancer or cervical intraepithelial neoplasia lesions) that the risk of cervical cancer and lesions may continue. Screening after 50 years of age was therefore suggested to continue at regular screening intervals until two consecutive negative screening results after 50 years. Conditional recommendations were made for screening intervals based on modelled evidence showing that three- or five-year screening intervals with HPV DNA testing (or cytology or VIA) may provide greater benefits, but there may be more treatments and therefore harm compared with a longer interval.

Conditional recommendations were made for HPV DNA testing 12 months after treatment and after a negative triage test, regardless of initial screening test, since there may be greater benefits and less harm.

HPV vaccines

HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer. Recommended target population for preventing cervical cancer: girls aged 9–14 years, before becoming sexually active *(127)*. A three-dose schedule (0, 1–2 and 6 months) should be used for all vaccinations initiated at 15 years and older, including those younger than 15 years known to be immunocompromised and/or living with HIV (regardless of whether they are receiving ART) *(127)*. Screening for HPV infection or HIV infection before HPV vaccination is not necessary *(127)*.

Additional recommendations *(126)*

Low-certainty evidence from a systematic review found that there may be little to no difference in the recurrence rate of adenocarcinoma in situ with cold-knife conization or electrosurgical excision or in the incidence of complications such as major infection and bleeding and found that more women may have premature deliveries in subsequent pregnancies following cold-knife conization compared with electrosurgical excision. The studies included in the systematic review did not confirm HIV status, but the Guideline Development Group agreed that the data could be extrapolated to women living with HIV and applied directly. Cold-knife conization is performed in the operating theatre, so access to cold-knife conization may be limited in some settings, more costly and less preferred by women compared with large loop excision of the transformation zone. In addition, greater expertise may be needed for successful electrosurgical excision.

WHO guidelines for implementing these recommendations are expected in late 2021.

6.10 Noncommunicable diseases

Recommendation (2016)

Assessment and management of cardiovascular risk should be provided for all individuals living with HIV according to standard protocols recommended for general population *(conditional recommendation, very-low-certainty evidence).*[a]

Good practice statement (2016)

Strategies for the prevention and risk reduction of cardiovascular diseases by addressing modifiable factors such as blood pressure, smoking, obesity status, unhealthy diet and lack of physical activity should be applied to all people living with HIV.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (51).*

[a] The WHO Package of Essential Noncommunicable (PEN) disease interventions for primary health care (128) in low-resource settings targets the following populations for cardiovascular disease screening: age older than 40 years, smokers, people with known hypertension or diabetes, waist circumference (>90 cm for women and >110 cm for men) and family history of diabetes or premature cardiovascular disease.

Background and rationale

Noncommunicable diseases, including hypertension, cardiovascular disease, renal disease, cancer, chronic respiratory disease, diabetes and mental health disorders, account for 63% of global deaths *(129)*. Low- and middle-income countries bear 86% of the burden of noncommunicable diseases *(129)*. Compared with the general population, people living with HIV have increased risk of developing a range of chronic noncommunicable diseases, including cardiovascular disease, hypertension, diabetes, chronic obstructive pulmonary disease, kidney disease and cancer *(130–135)*.

The intersection of HIV and noncommunicable diseases is strongly influenced by increasing survival because of effective ART, lifestyle factors, ART adverse events, chronic immune activation caused by HIV and other disease conditions associated with ageing *(136,137)*. Cardiovascular disease is now one of the leading causes of non-AIDS-related morbidity and mortality among people living with HIV. Both HIV and noncommunicable diseases require health systems that can deliver effective acute and chronic care and support adherence to treatment. Chronic HIV care provides the opportunity for assessing, monitoring and managing noncommunicable diseases, especially through primary care. Integrating interventions such as nutrition assessment, dietary counselling and support, smoking cessation, exercise promotion, blood pressure monitoring and – when available – cholesterol management as part of HIV care can help to reduce the risks of noncommunicable diseases among people living with HIV and improve HIV treatment outcomes *(138,139)*.

WHO has defined a package of essential noncommunicable disease interventions *(128)* and provides recommendations on assessing and managing the major noncommunicable diseases from the primary care level to the district hospital level. The interventions are mainly focused on assessing and managing cardiovascular disease risk, including high blood pressure, type 2 diabetes, chronic respiratory diseases (asthma and chronic obstructive pulmonary disease) and early identification of breast and cervical cancer.

Several studies have demonstrated that people living with HIV have increased risk of cardiovascular diseases compared with HIV-negative people in the same age ranges and that cardiovascular disease accounts for an increasing proportion of mortality observed in this population *(140,141)*. Large cohort studies have confirmed that the risk of both myocardial infarction and cerebrovascular disease is 40–70% greater among people living with HIV than among age- and sex-matched HIV-uninfected controls *(142–147)*. This association has been reported both among people receiving ART and among those who are treatment-naive. Similar findings have also been reported for children and adolescents with HIV *(148)*. The mechanisms underlying the association between HIV and cardiovascular disease are multifactorial and include HIV-related chronic immune activation and inflammation, immunodeficiency and elevated burdens of traditional cardiovascular disease risk factors among people living with HIV *(149–152)*.

Findings from observational studies have shown that the role of ART in cardiovascular disease risk and exposure to some classes of ARV drugs (PIs) causes lipid abnormalities and may increase the risk of premature cardiovascular disease *(153–156)*. Associations between NRTIs and the risk of cardiovascular disease remain the subject of debate. Although recent and cumulative exposures to some NRTIs such as ABC have been associated with increased relative risk for cardiovascular disease *(157–160)*, other reviews have not found such an association *(161,162)*. Several studies have demonstrated an increased risk of cardiovascular disease events among people discontinuing ART and people with detectable viral load *(163)*. It has been hypothesized that the increased attributable risk among people living with HIV results from increased immune activation and chronic inflammation, which remain abnormally high among people living with HIV even after suppression of viral loads *(149,151)*. Both are associated with preclinical and clinical atherosclerosis. The overall beneficial role of ART on HIV morbidity and mortality has therefore been demonstrated to outweigh the potential risk of cardiovascular disease for people living with HIV.

Cardiovascular disease screening for people living with HIV has been recommended in several HIV clinical guidelines, and several risk tools for calculating cardiovascular disease probability have been used *(164–168)*. Several studies have demonstrated that incorporating routine cardiovascular disease screening for people living with HIV could improve health outcomes and be cost effective *(169–171)*.

A systematic review on using validated tools to identify the people at highest cardiovascular disease risk for primary prevention shows that there is potential to lower cardiovascular disease mortality and the incidence of cardiovascular events; this was especially evident in studies with high-intensity interventions *(172)*. However, despite the overall consensus that the current cardiovascular disease screening tools designed for the general population have a moderate discriminatory power to determine which people living with HIV have a high risk for cardiovascular disease events or eligibility for therapeutic interventions, these tools frequently underestimate the cardiovascular disease risk of people living with HIV and need to be adjusted or validated in the HIV populations *(173–180)*. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group has described a cardiovascular disease risk algorithm that incorporates some HIV-specific factors such as CD4 cell count and ARV drug use that has reported better accuracy in predicting serious cardiovascular disease events *(181–183)*. Although this is an important step towards improving cardiovascular disease risk prediction, it still has limitations because the study populations – all in high-income settings – have different genetic and behavioural cardiovascular disease risk profiles than most people living with HIV in the world. In addition, as in the case of studies reporting less direct risk predictions, the D:A:D: instrument can also significantly overestimate and underestimate cardiovascular disease risk *(176–178)*.

Implementation considerations

No specific WHO recommendation for the management of cardiovascular disease in people with HIV has been made in previous guidelines. However, since 2010, WHO has defined a package of essential noncommunicable disease interventions (WHO PEN), along with recommendations on screening for and treating noncommunicable diseases in the general population. WHO PEN *(128)* has several programmatic advantages in resource-limited settings, since it integrates other major noncommunicable diseases in addition to cardiovascular disease, can be implemented in primary health care, can be managed by non-physicians, consists of a minimal package and has good discrimination to identify those with high cardiovascular disease risk. The systematic review did not identify any studies assessing the impact or use of WHO PEN interventions for people living with HIV with any outcomes relevant to low- and middle-income countries. Studies on WHO PEN–based interventions in the general population from low- and middle-income countries were found, showing that the PEN protocol and universal risk assessment are cost-effective *(184–186)*. Further, an evaluation of the short-term outcomes of PEN in pilot districts indicated a significant reduction of cardiovascular disease risk and increased healthy lifestyle of the target population *(184)*.

Disparities in cardiovascular disease care among people living with HIV have been reported. In two studies, people living with HIV were significantly less likely to receive aspirin for cardiovascular disease prevention than those without HIV *(187,188)*. Other data on medical management and outcomes following acute myocardial infarction showed that people living with HIV received significantly fewer cardiovascular procedures and/or therapeutics than people without HIV *(189)*. Regularly assessing and managing cardiovascular disease risk among people living with HIV are expected to result in better and more equitable care.

One major remaining barrier to equitable access to cardiovascular disease prevention and care for people living with HIV is the lack of high-quality data assessing proven cardiovascular disease therapies in this population. For example, prospective trials on using statins for people living with HIV have generally been underpowered and have not assessed hard clinical endpoints *(190).*

Integrated multi-disease campaigns conducted in Lesotho and Uganda that included cardiovascular disease screening and HIV testing demonstrated the feasibility of integrated screening for communicable and noncommunicable diseases in community-based HIV programmes *(191,192)*. Improved diagnosis and linkage to care for cardiovascular disease conditions have been shown to also improve linkage to HIV care and ART *(193)*. Cardiovascular disease and HIV integration pilot services have been implemented in Kenya, Nigeria and Zambia since 2012 and shown to be feasible and acceptable, with cardiovascular disease integration implemented within the context of an HIV chronic care model *(194)*.

Research gaps

Further research is needed to unravel the complex pathophysiology of atherogenesis among people living with HIV, to elucidate the relationship between traditional and HIV-associated cardiovascular disease risk factors and to investigate how ART alters these interactions. Studies on how early ART affects cardiovascular disease development, especially among adolescents and children living with HIV, are also needed. Studies are needed on cardiovascular disease treatments, such as ACE inhibitors and statins, which may be beneficial in reducing inflammation related to HIV. Clinical studies to assess methods of risk prediction and risk-reduction strategies for cardiovascular disease applicable to people living with HIV would be of great use. There is a need to validate simplified cardiovascular disease screening protocols

and risk assessment algorithms, appropriate to geographical regions, that include HIV-specific risk factors to improve accuracy. Using cardiovascular disease co-therapies such as statins, aspirin, antihypertensive drugs and metformin and measuring their impact on HIV mortality are also important. Assessments of the unique pathophysiology, related risk factors and optimal management of downstream cardiovascular disease complications associated with HIV, such as heart failure and malignant arrhythmia, are also needed. Such studies should be conducted in both high-income and resource-limited countries. In limited cohort data, integrase inhibitors have been reported to be associated with a decreased risk of cardiovascular disease. These findings require validation in other cohorts and with longer follow-up *(195)*. Although integrase inhibitor–based regimens are highly efficacious for suppressing viral loads, they appear to cause more weight gain and treatment-emergent obesity than non-integrase inhibitor–based regimens and may increase the risk of weight-related comorbidities. More studies are needed to understand the pathogenesis of weight gain with INSTIs among people living with HIV to prevent this serious complication *(196)*.

6.11 Mental health among people living with HIV

Recommendation (2016)

Assessment and management of depression should be included in the package of HIV care services for all individuals living with HIV *(conditional recommendation, very-low-certainty evidence).*

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (51).*

Introduction

People living with HIV are at high risk of mental, nervous system and substance use disorders *(197)*. A systematic review from both from low- and high-income countries show that depression is one of the most prevalent mental health comorbidities in people living with HIV *(198,199)*. In a 2019 systematic review of the burden of depression among people living with HIV in Africa, the overall prevalence estimates were 36% (95% CI 32–41%) for depressive disorders and 15% (95% CI 12–18%) for probable major depressive disorders *(200)*. Another 2019 systematic review reported the prevalence of depression among people living with HIV globally as 31% (95% CI 28–34%).

A systematic review conducted in 2015 reported depression prevalence rates as high as 80% among people living with HIV but with wide variation across studies that is attributed to the screening and diagnostic criteria used *(201)*. Depressive symptoms have been reported as common in many studies in sub-Saharan Africa, where the HIV burden is also high *(202,203)*.

People living with HIV who have depression are less likely to achieve optimal treatment adherence. Although chronic HIV care settings provide an opportunity to detect and manage depression among people living with HIV, it is often overlooked and unrecognized by health-care providers. Treatment or lack of treatment for mental health disorders can affect general health, adherence to ARV drugs and retention in care and may lead to potential side-effects and drug–drug interactions being overlooked *(201,204–207)*.

The *mhGAP intervention guide for mental, neurological and substance use disorders in non-specialized health settings: Mental Health Gap Action Programme (mhGAP), version 2 (208)* provides evidence-informed comprehensive guidelines on the diagnosis and management of

a range of mental, nervous system and substance use disorders, including developmental and behavioural disorders among children and adolescents, with a focus on nine priority mental health conditions, including diagnosing and managing people with depression. Key updates include a simplified clinical assessment algorithm for follow-up and the inclusion of new modules; an implementation module of necessary infrastructure and resources and revised modules on psychoses, behavioural disorders, disorders caused by substance use and child and adolescent mental health *(208)*. Implementing mhGAP through primary care would improve the detection and management of depression among adults compared with standard-of-care approaches *(209)*.

A systematic review conducted to support the guideline update in 2015 aimed to determine whether routine screening and management of depression (specifically with mhGAP criteria) improve ART adherence and treatment outcomes among people living with HIV *(51,208)*. No studies were identified explicitly reporting on mhGAP for this specific population.

Indirect evidence from a systematic review on the accuracy of using screening tools to identify depression among people living with HIV in all settings identified 18 studies, using 25 different screening instruments, compared with criterion standards for diagnosing depression *(51,208)*. Multiple index test and criterion standards were assessed, and the review evaluated each test's area under the curve as a summary measure of accuracy (area under the curve above 0.9 is considered to be highly accurate; 0.7 to 0.9 to be moderately accurate; and 0.51 to 0.69 to be of low accuracy) *(207)*. Although several instruments showed very good or even excellent performance diagnosing depression among people living with HIV, the overall certainty of evidence is very low. The Guideline Development Group, considering acceptability and feasibility from end-users and lack of harm, made a conditional recommendation.

Although depression is more common among people living with HIV than in the general population, there is less consistent and limited evidence to show that managing depression improves HIV treatment outcomes. However, management of depression improves the mental health and general well-being of people living with HIV.

The limited data on HIV and mental health service delivery models indicate that integration supports efficiency and does not increase the costs of care. A narrative review from sub-Saharan Africa suggests that integrating mental health care into existing health systems is an effective and cost-efficient approach to expand access to mental health services for people living with HIV in resource-limited settings *(210)*. There is also an ongoing study on the cost–effectiveness of screening and treating people living with HIV for depression in sub-Saharan Africa *(211)*. However, more evidence is needed on effective models of integrating HIV and mental health services in various settings *(212)*.

A survey of national HIV programme managers found that 38% of respondents reported that mental health screening is performed in some HIV care settings with referral for treatment when indicated *(51)*. Forty-three per cent did not have mental health screening and treatment available for people living with HIV. None of the countries reported countrywide implementation of mental health screening and treatment services in all HIV care settings. The top three challenges identified by programme managers for integrating mental health services in HIV care settings are shortage of human resources, skills and capacity of health-care providers and lack of funding. WHO estimates that up to 85% of people with severe mental disorders and 56% of people with depression in low- and middle-income countries do not have access to treatment *(213)*.

Implementation considerations

Screening for depression may support adherence to ART, retention in care, suppression of viral loads and improve quality of life and, if implemented, depression should be managed according to national standards or mhGAP. Integration or linkage to the mental health services

should be implemented in the settings in which health-care infrastructure and trained human resources are available. Implementing treatment for depression among people living with HIV may require task sharing, building health-care worker capacity, national adaptation of screening tools and simplifying tools for use by non-specialized primary care providers.

Research gaps

There are several research gaps related to screening and treating people living with HIV for mental health disorders and depression:

- the accuracy of current estimates of HIV and depression because of the wide variability in reports, with packages of care for common mental disorders likely to be most effective among people living with HIV in low- and middle-income countries;
- the long-term impact of depression interventions in relation to HIV outcomes; and
- the optimal time-points for mental health interventions.

6.12 Drug use and drug use disorders

People who use drugs may experience a range of disorders related to drug use, including drug dependence, intoxication, withdrawal and overdose. Injecting drug use is associated with a range of diseases and infections, including HIV, viral hepatitis, TB, septicaemia and bacterial endocarditis.

WHO, UNODC and UNAIDS recommend a comprehensive package of interventions for HIV prevention, treatment and care for people who inject drugs, including needle and syringe programmes, opioid substitution therapy, HIV testing and counselling, ART, preventing and treating sexually transmitted infections, condom programmes, targeted behaviour change communication, preventing and treating viral hepatitis and preventing, diagnosing and treating TB. More recently, WHO updated this package to include community distribution of naloxone to manage opioid overdose as well as a set of enabling interventions to overcome the structural barriers for people who use drugs and other key populations to access these health interventions. These enabling interventions include revising laws and legislation that criminalize the consumption and possession of drugs and address violence, stigma and discrimination in health-care settings.

Although the focus with HIV has been injecting opioids, a link is becoming more evident between using other drugs such as amphetamine-like stimulants and sexual risk and transmission of HIV *(214)*.

A form of sexualized drug use is also seen in subgroups of men who have sex with men, often referred to as chemsex, with increased risk of HIV and sexually transmitted infections, including HCV transmission.

6.13 Sexually transmitted infections

Recommendations

Sexually transmitted infection and family planning services can be integrated within HIV care settings *(conditional recommendation, very-low-certainty evidence).*

For men who have sex with men and transgender people (2011)

Offering periodic testing for asymptomatic urethral and rectal *N. gonorrhoeae* and *C. trachomatis* infections using NAAT is suggested over not offering such testing for men who have sex with men and transgender people *(conditional recommendation, low-certainty evidence).*

Not offering periodic testing for asymptomatic urethral and rectal *N. gonorrhoeae* infections using culture is suggested over offering such testing for men who have sex with men and transgender people *(conditional recommendation, low-certainty evidence).*

Offering periodic serological testing for asymptomatic syphilis infection to men who have sex with men and transgender people is strongly recommended over not offering such screening *(strong recommendation, moderate-certainty evidence).*

For sex workers and their clients in low- and middle-income countries (2012)

We suggest offering periodic screening for asymptomatic sexually transmitted infections to female sex workers *(conditional recommendation, low-certainty evidence).*

We suggest offering female sex workers, in settings with high prevalence and limited clinical services, periodic presumptive treatment for asymptomatic sexually transmitted infections *(conditional recommendation, moderate- to high-certainty evidence).*

For pregnant women (2017)

The WHO sexually transmitted infection guideline recommends screening all pregnant women for syphilis during the first antenatal care visit *(strong recommendation, moderate-certainty evidence).*

This recommendation applies to all settings, including settings with high or low prevalence of syphilis.

Sources: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (51); Guidelines: prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender populations: recommendations for a public health approach (215); Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach (216); and WHO guidelines on syphilis screening and treatment for pregnant women (217).*

Recommendations for the management of symptomatic sexually transmitted infections (2021)

Management of urethral discharge

For people who present with urethral discharge from the penis, management is recommended to be based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit *(strong recommendation, moderate-certainty evidence).*

Management of vaginal discharge

For people who present with vaginal discharge, WHO recommends treatment for *N. gonorrhoeae* **and/or** *C. trachomatis* **and/or** *T. vaginalis* **on the same visit. WHO suggests treatment based on the results of quality-assured molecular assays for** *N. gonorrhoeae* **and/or** *C. trachomatis* **and/or** *T. vaginalis*. **In settings in which treatment based on the results of molecular assay in the same visit is not feasible or that have limited or no molecular testing, WHO suggests treatment based on testing with quality-assured rapid point-of-care tests or on syndromic treatment** *(strong recommendation, moderate-certainty evidence).*

WHO suggests treating for bacterial vaginosis if vaginal discharge is present (for example, tenacious or thin) or based on the results of microscopy, if available *(conditional recommendation low-certainty evidence).*

WHO suggests treating for candidiasis, where indicated by type of discharge (such as curd-like with vaginal itching) or by the results of microscopy, if available *(conditional recommendation low-certainty evidence).*

For management of women with lower abdominal pain

For sexually active women who present with lower abdominal pain, WHO suggests assessing for pelvic inflammatory disease and treating syndromically.

For sexually active women with lower abdominal pain with either of the following features on clinical examination (bimanual palpation):

- cervical motion tenderness; or
- lower abdominal tenderness:

WHO suggests the following.

- **Treat for pelvic inflammatory disease on the same visit. Test for infection with** *N. gonorrhoeae* **and** *C. trachomatis* **and, if available,** *Mycoplasma genitalium*, **to support partner management when tests are available** *(conditional recommendation, low-certainty evidence).*

Management of genital ulcer disease, including anorectal ulcers

For people who present with genital ulcers (including anorectal ulcers), WHO recommends treatment based on quality-assured molecular assays of the ulcer. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit *(strong recommendation, moderate-certainty evidence).*

Recommendations for the management of symptomatic sexually transmitted infections (2021) (continued)

Management of anorectal discharge

For people who present with anorectal discharge and report receptive anal sex, WHO recommends management based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommends syndromic treatment to ensure treatment on the same day of the visit *(strong recommendation, moderate-certainty evidence).*

Good practice for men includes:

- taking a medical and sexual history and assessing risk for sexually transmitted infections;
- performing a physical examination of the genital and anal areas;
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines;
- if symptoms persist at review, good practice includes checking partner notification and treatment history; and
- for people with recurrent or persistent urethral discharge, referring people to a centre with laboratory capacity to diagnose infection with *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and *T. vaginalis* and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium*.

Good practice for women includes:

- taking a medical and sexual history and assessing risk for sexually transmitted infections;
- performing a physical examination, including abdominal and pelvic examination to assess for pelvic inflammatory disease, surgical conditions or pregnancy and external vulvo-vaginal examination to visualize any lesions, overt genital discharge or vulval erythema and excoriations;
- bimanual digital examination of the vagina to (1) assess for cervical motion tenderness or pain with palpation of the pelvic area to exclude pelvic inflammatory disease; and (2) assess for the presence of vaginal discharge and the colour and consistency of the discharge on the glove;
- offering HIV and syphilis testing and other preventive services as recommended in other guidelines; and
- for people with recurrent or persistent vaginal discharge, referring to a centre with laboratory capacity to diagnose infection with *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, *T. vaginalis* and bacterial vaginosis and to test for antimicrobial-resistant *N. gonorrhoeae* and *M. genitalium* (if there is a test) or for a specialist's assessment (sexually transmitted infection expert and physician or a gynaecologist), when no such testing is available in primary health care centres.

Sources: *Guidelines for the management of symptomatic sexually transmitted infections (218).*

Introduction

The syndemics model of health describes the interaction of two or more concurrent or sequential epidemics and the additive effect, with each one intensifying the others *(219)*. There is a high co-prevalence of HIV and the other sexually transmitted infections, particularly in vulnerable populations. Many of these infections are asymptomatic, especially among women *(220)*.

Substantial evidence indicates that sexually transmitted infections increase HIV transmissibility and the risk of acquiring HIV by as much as 2–3 times in some populations *(221,222)*. It has also been shown that infection with *N. gonorrhoeae* substantially increases shedding of HIV-1 from the male genital tract in seminal fluid *(223)*. Genital herpes (HSV-2) almost triples the risk of acquiring HIV for both men and women *(224,225)*. HIV increases the infectiousness and severity of sexually transmitted infections *(226)*. HIV-seropositive women are at high risk of infection with human papillomavirus (HPV), including oncogenic HPV types *(227)*. To reduce HIV transmission and optimize sexual and reproductive health, sexually transmitted infections need to be diagnosed and treated as a priority (228). Efforts should therefore be taken to strengthen sexually transmitted infection prevention, screening, diagnosis and treatment.

In a systematic review, the median prevalence of sexually transmitted infections among people living with HIV was 12.4%. The most common sexually transmitted infections were syphilis, gonorrhoea, chlamydia and trichomoniasis *(229)*. Modelling has estimated that 10% of the cases in which gay men and other men who have sex with men acquire HIV are attributable to increased susceptibility because of *N. gonorrhoeae* or *C. trachomatis* infection *(230)*. Reports in many settings indicate high sexually transmitted infection prevalence among users of PrEP at baseline screening and high incidence while taking PrEP. The reports also include high rates of gonorrhoea, especially among men who have sex with men *(231)*.

For people living with HIV, a holistic and comprehensive approach to sexual and reproductive health and rights includes appropriate sexually transmitted infection services. People living with HIV should be screened and treated for sexually transmitted infections. Men who have sex with men and transgender people with symptomatic sexually transmitted infections should seek and be offered syndromic management and treatment, in line with existing WHO guidance.

Management

Symptomatic cases should either be managed syndromically and where feasible, etiological diagnosis obtained *(218)*. To prevent future sexually transmitted infections, the promotion and provision of safer sex practices, including condom use, should be reenforced. Appropriate sexually transmitted infection treatment, including partner management, should be ensured. For people who have urethral discharge, vaginal discharge, lower abdominal pain, anorectal discharge or genital ulcer, WHO recommends management based on the results of quality-assured molecular assays. However, in settings with limited or no molecular tests or laboratory capacity, WHO recommend syndromic treatment to ensure treatment on the same day of the visit. Specific recommendations are available for each syndrome *(232)*.

Sexually transmitted infection treatment for sex workers, men who have sex with men and transgender people

Anorectal symptoms and anorectal sexually transmitted infections are prevalent among men who have sex with men, female sex workers, transgender people and heterosexual women who engage in anal sexual intercourse. Asymptomatic anorectal infections are not uncommon, although precise data are scarce. The people at highest risk of asymptomatic anorectal infections

are men who have sex with men, male and female sex workers, transgender people and women who have had receptive anal intercourse with men with sexually transmitted infections. For syndromic diagnosis and management, these infections have been grouped under anorectal infections. Anorectal infections may be associated with anorectal pain, itching, discharge, bleeding, sensation of rectal fullness, tenesmus, constipation and mucus streaking of stools.

Recommendations for the treatment of syphilis among pregnant women and of congenital syphilis have been previously published, updated in 2016 *(233)* and reprinted in 2017 *(217)*.

Implementation considerations

A key approach to increasing the coverage of sexually transmitted infection services for people living with HIV is integration or linkage of these services within HIV care and treatment settings *(51)*. It is necessary to promptly adopt service delivery models that integrate a people-centred approach to address sexually transmitted infections among people living with HIV.

Integration and linkage between HIV and sexual and reproductive health services require approaches that engage those at greatest risk for HIV and other sexually transmitted infections in any interventions and programmes. This will increase access to appropriate testing, linkage to treatment and further strengthening of preventive services. Frequently, stigma and discrimination result in reduced health-seeking behaviour, delaying diagnosis and effective partner notification and, consequently, impeding public health efforts to control the sexually transmitted infection and HIV epidemics. Health-care providers providing HIV prevention and treatment services need to provide culturally competent and sensitive sexually transmitted infection care, so that vulnerable populations seek clinical services more readily.

Research gaps

The challenge for researchers, clinicians and public health officials is to understand how best to promote sexual health *(234)*. The improvements in HIV treatment, diagnostic capabilities for HIV and other sexually transmitted infections and educational digital media create new challenges and opportunities for key stakeholders, including civil society, to limit the spread of sexually transmitted infections while respecting individual decisions about sexual expression.

6.14 Vaccines for people living with HIV

Immunizations are an important component of the HIV care package in many international guidelines, and people living with HIV should be assessed for eligibility for vaccination at all stages of care *(235–237)*. Vaccines usually have better safety and efficacy among people living with HIV who are receiving ART and those without significant immunosuppression, notably when the CD4 cell count is above 200 cells/mm^3. People with more severe immunosuppression may be at higher risk of complications from some live attenuated vaccines. Inactivated vaccines, although safe, can be less effective among these people and may require supplemental doses or revaccination after ART-induced immune reconstitution. Transient increases in plasma HIV-RNA load have also been reported after the administration of several vaccines. Available evidence indicates that these transient increases are not clinically significant *(238,239)*.

In general, HIV-exposed infants, children and adolescents with HIV should receive all vaccines under routine vaccination according to recommended national immunization schedules *(240,241)*.

COVID-19 vaccination

Many of the COVID-19 vaccine studies have included a few people living with HIV in their trials. Despite limited data, the available information suggests that current WHO-recommended COVID-19 vaccines are safe for people living with HIV *(242)*. No interactions have been reported between COVID-19 vaccines and ARV drugs, which people living with HIV should continue to take after vaccination to maintain health.

The source of most recommendations for vaccinating people living with HIV is WHO position papers and summary tables published in 2017 and 2018 *(80,127,243–254)*. The position papers include guidance on BCG, HPV, HBV, measles, dengue, rubella, typhoid, pneumococcal and cholera vaccination for people living with HIV (Table 6.6).

Table 6.6 HIV-specific guidance for selected vaccines from WHO vaccine position papers

BCG	If people living with HIV, including children, are receiving ART, are clinically well and immunologically stable (CD4% >25% for children five years old), they should be vaccinated with BCG. Neonates born to women of unknown HIV status should be vaccinated since the benefits of BCG vaccination outweigh the risks. Neonates of unknown HIV status born to women living with HIV should be vaccinated if no clinical evidence suggests HIV infection, regardless of whether the mother is receiving ART. For neonates living with HIV confirmed by early virological testing, BCG vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable (CD4 >25%). Source: World Health Organization *(244)*.
HBV	In a 2014 systematic review addressing the immune responses among people living with HIV to HBV vaccine with standard versus high dosage, six studies among adults found higher peak anti-HBs antibody titres after the higher dosage compared with the standard dosage vaccines but no clear difference in the proportion of adults with protective antibodies up to five years after vaccination. Source: World Health Organization *(80)*.
DTP-containing vaccines (diphtheria, tetanus and pertussis)	Tetanus toxoid–containing vaccines are suitable for immunocompromised people, including people living with HIV, but the immune response may be lower than for fully immunocompetent people. All children living with HIV should be vaccinated against tetanus following the vaccine recommendations for the general population. Source: World Health Organization *(245–247)*.
Measles	Measles vaccination should be routinely administered to potentially susceptible, asymptomatic children and adults living with HIV. Vaccination may even be considered for those with symptomatic HIV infection if they are not severely immunosuppressed according to conventional definitions. In areas with a high incidence of both HIV infection and measles, an initial dose of measles-containing vaccine may be offered as early as age six months. The two routine doses of measles-containing vaccine should then be administered to these children according to the national immunization schedule. A supplementary dose of measles-containing vaccine should be given to infants from six months of age known to be HIV-infected or exposed. Source: World Health Organization *(248)*.

Table 6.6 HIV-specific guidance for selected vaccines from WHO vaccine position papers (continued)

HPV	HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer. Recommended target population for the prevention of cervical cancer: girls aged 9–14 years, before becoming sexually active. A three-dose schedule (0, 1–2 and 6 months) should be used for all vaccinations initiated among those older than 15 years of age, including those younger than 15 years known to be immunocompromised and/or living with HIV (regardless of whether they are receiving ART). Screening for HPV infection or HIV infection before HPV vaccination is not necessary. Source: World Health Organization *(127)*.
Cholera	Appropriate case management, water, sanitation and hygiene interventions, surveillance and community mobilization remain the cornerstones of cholera control. Vaccination should be implemented in relevant settings as part of comprehensive cholera control strategies or while other activities are being developed. During humanitarian emergencies with a risk of cholera, but without a current cholera outbreak, vaccination with oral cholera vaccines should be considered as an additional preparedness measure for outbreak prevention, depending on the local infrastructure (capacity to organize a vaccination campaign). Pregnant and lactating women and people living with HIV should be included in oral cholera vaccine campaigns since there is a high potential benefit and minimal risks. Source: World Health Organization *(249)*.
Dengue	No data are available on the safety of the first licensed dengue vaccine, CYD-TDV, for individuals with immunodeficiency or HIV infection. The manufacturer stipulates that vaccination is contraindicated for individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function. Source: World Health Organization *(250)*.
Pneumococcal conjugate vaccines	Infants living with HIV and preterm neonates who have received their three primary vaccine doses before 12 months of age may benefit from a booster dose in the second year of life. Source: World Health Organization *(251)*.
Rubella	Rubella-containing vaccines should not be given to anyone who has severe immunodeficiency, including individuals with symptomatic HIV infection and AIDS. Source: World Health Organization *(252)*.
Typhoid	There are currently no data on typhoid-containing vaccine for immunocompromised people and people living with HIV. Although the typhoid Vi-polysaccharide vaccine is safe for people living with HIV, the induction of protective antibodies is directly correlated to CD4 cell count. Oral typhoid vaccine Ty21a can be administered to immunologically stable people living with HIV (CD4 >25% for children younger than five years, CD4 cell count ≥200 cells/mm^3 if five years and older). Ty21a is not recommended for individuals with a known depression of cell-mediated immunity, although adverse effects have not been reported. There is no risk for immunocompromised household contacts of the people vaccinated with Ty21a. Source: World Health Organization *(253)*.

Further information on other vaccinations comes from a scoping review *(255)* that aims to identify and evaluate new evidence on using selected vaccines for children living with HIV concerning vaccine safety, efficacy, dosing and immunization schedule together with the effect of immune status and ART at the time of vaccination.

The scoping review for children living with HIV sought to identify safety and efficacy studies published since the last published systematic review (2012) of immunization of children living with HIV *(254)*. The final scoping review included 19 articles.

The scoping review focused on:

- vaccines recommended for all children: diphtheria, tetanus, oral polio, pertussis, *Haemophilus influenzae* type B, rotavirus, pneumococcal conjugate and rubella;
- vaccines recommended for children in some high-risk populations: dengue, rabies, typhoid, meningococcal and hepatitis A;
- vaccines for children receiving vaccinations from immunization programmes with certain characteristics: varicella, influenza and mumps; and
- vaccines for children residing in certain regions: Japanese encephalitis, tick-borne encephalitis and yellow fever.

None of the studies assessing safety showed any significant difference in side-effects among children living with HIV compared with uninfected controls. Although in most of the studies, children living with HIV had lower antibody levels in response to vaccination, the proportion of children reaching the seroprotective levels was similar compared with uninfected children for most of the vaccines, except for pertussis vaccine and oral polio vaccine, for which children living with HIV reached lower levels. Eight of the 17 included studies had a sample size of 50 or fewer children living with HIV, most of whom were receiving ART.

Immunization against some diseases such as influenza, HBV, pneumococcal disease and tetanus is frequently indicated for adults living with HIV. Other immunizations may be recommended based on age, risk factors or travel plans.

For currently recommended vaccination schedules and detailed guidance on immunization for all age groups, see WHO recommendations for routine immunization – summary tables *(254)*.

WHO has position papers on each vaccine and statements about them for people living with HIV *(243–253)*.

6.15 HIV-related skin and oral conditions

HIV infection increases the prevalence and severity of skin and oral diseases, especially when the person's CD4 cell count declines below 200 cells/mm^3. As a result, skin and oral conditions affect up to 90% of adults and children with HIV in resource-limited settings *(51)*. Adverse drug reactions of the skin are also 100 times more common among people living with HIV than among the general population, and their prevalence increases as immunodeficiency worsens. Immune reconstitution inflammatory syndrome occurs in 10–25% of people living with HIV starting ART. Cutaneous manifestations of immune reconstitution inflammatory syndrome, such as seborrhoeic dermatitis, anogenital herpes, acne, tinea, folliculitis, Kaposi's sarcoma, herpes zoster, genital warts, molluscum contagiosum and pityriasis versicolor, are common,

occurring among up to 50% of people living with HIV commencing ART with a low CD4 cell count *(256)*.

Skin and oral manifestations of HIV infection can aggravate stigma in some societies as physical signs in the form of skin diseases, such as papular pruritic eruption, that suggest the possibility of HIV infection could make the affected person more vulnerable to discrimination *(51)*.

WHO guidelines *(257)* describe common HIV-related skin disorders based on the burden of disease among adults and children living with HIV and the availability of evidence and effective interventions. These are Kaposi's sarcoma, seborrhoeic dermatitis, papular pruritic eruption, eosinophilic folliculitis, tinea infections, herpes zoster, scabies, molluscum contagiosum, oropharyngeal candidiasis, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Certain systemic diseases, such as Kaposi's sarcoma, may initially be noted on the skin and may require urgent ART to reduce mortality. Others, while not always a major cause of mortality, can be a source of severe morbidity through, for example, itching that provokes scratching, secondary infections, disfigurement, sleep disturbance and mental stress. Candidiasis can cause pain on swallowing, limiting a person's ability to take ARV drugs.

Because of a lack of services to promptly diagnose and manage skin and oral conditions, many people attempt to conceal the skin disease or avoid social contact. These could affect their health-seeking behaviour, negatively affecting their self-esteem and quality of life. Skin and oral conditions are one of the most common management problems faced by health-care workers caring for people living with HIV.

In 2014, WHO released guidelines for treating common HIV-associated skin and oral conditions in low- and middle-income countries *(257)*. They are applicable for all adults, pregnant women, adolescents and children living with HIV and recommend HIV testing for everyone with unknown HIV status presenting with the discussed skin conditions, and if the HIV status is known, they should be evaluated to initiate ART.

ART is the initial treatment of choice for several of these conditions, such as Kaposi's sarcoma, papular pruritic eruption, eosinophilic folliculitis and molluscum contagiosum.

6.16 Nutritional care and support

Low energy intake combined with increased energy demands from HIV infection *(258–260)* and related opportunistic and other infections may lead to HIV-related weight loss and wasting. In addition, an altered metabolism, reduced appetite and higher incidence of diarrhoea may lower nutrient intake and absorption and lead to nutrient losses. These effects may all be compounded in low-income, food-insecure contexts. Low body mass (BMI less than 18.5 kg/m^2 for adults), weight loss and wasting in children are all independent risk factors for HIV disease progression and mortality *(261,262)*. Nutritional assessment (anthropometry, clinical and dietary assessment), counselling and support should be an integral component of HIV care and conducted at enrolment in care and monitored across the care continuum. Malnourished people with HIV, especially in food-insecure contexts, may require food supplements in addition to ART to support nutritional recovery. Weight loss or failure to regain or maintain a healthy weight at any stage of HIV infection, including while receiving ART, should trigger further assessment and appropriate interventions.

Nutrition for children living with HIV

For infants and young children, ensuring optimal feeding, including exclusive breastfeeding for the first six months of life, followed by complementary feeding and breastfeeding through at least 24 months, within the context of HIV is important in all settings in which the prevalence

of HIV is high and diarrhoea, pneumonia and undernutrition are common causes of infant and child mortality. Guidance on nutritional care for people living with HIV is summarized in section 6A of WHO's Essential nutrition actions: mainstreaming nutrition through the life-course *(263)*.

Nutritional assessment is essential to identify malnutrition and growth faltering early. Infants and children should undergo initial nutritional assessment (evaluation of nutritional status, diet and symptoms) and then be weighed and have height measured at each visit and monitored with reference to WHO or national growth curves. Growth monitoring should also be integrated into the assessment of response to ART *(264)*. If poor growth is identified, then further assessment should be performed to determine the cause and appropriate response planned. WHO guidelines *(265)* provide details on nutritional interventions.

6.16.1 Infant feeding in the context of HIV

Recommendations (2016)

Duration of breastfeeding by mothers living with HIV[a]

Mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (similar to the general population) while being fully supported for ART adherence (see Chapter 7 for interventions to optimize adherence) *(strong recommendation, low-certainty evidence for 12 months; very-low-certainty evidence for 24 months).*[b]

Remarks

In settings in which health services provide and support lifelong ART, including adherence counselling, and promote and support breastfeeding among women living with HIV, the duration of breastfeeding should not be restricted. Further, mothers living with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter and continue breastfeeding.

Recommendations (2016) (continued)

Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast-milk can be provided.

[a] This recommendation updates the component of the 2010 recommendation on which breastfeeding practices and for how long related to the duration of breastfeeding. The components of the 2010 recommendation on breastfeeding practices and stopping breastfeeding remain unchanged and valid.

[b] WHO-recommended breastfeeding is defined as: (1) initiating breastfeeding within the first hour of life; (2) exclusive breastfeeding for the first six months of life (that is, the infant only receives breast-milk without any additional food or drink, not even water); followed by (3) continued breastfeeding for up to two years of age or beyond (with the introduction of appropriate complementary foods at six months); and (4) breastfeeding on demand – that is, as often as the child wants, day and night.

Source: *Guideline: updates on HIV and infant feeding: the duration of breastfeeding, and support from health services to improve feeding practices among mothers living with HIV (266).*

Good practice statements (2010)

When mothers living with HIV do not exclusively breastfeed

Mothers living with HIV and health-care workers can be reassured that ART reduces the risk of postnatal HIV transmission in the context of mixed feeding. Although exclusive breastfeeding is recommended, practising mixed feeding is not a reason to stop breastfeeding in the presence of ARV drugs.

When mothers living with HIV do not plan to breastfeed for 12 months

Mothers living with HIV and health-care workers can be reassured that shorter durations of breastfeeding of less than 12 months are better than never initiating breastfeeding at all.

Source: *Guidelines on HIV and infant feeding: principles and recommendations for infant feeding in the context of HIV and a summary of evidence (266).*

Introduction

Breastfeeding is the cornerstone of child survival, nutrition and development and maternal health and is one of the foundations of child health, development and survival, especially where diarrhoea, pneumonia and undernutrition are common causes of mortality among children younger than five years. WHO recommends exclusive breastfeeding for the first six months of life, followed by continued breastfeeding with appropriate complementary foods for up to two years or beyond. The evidence for the long-term benefits of longer durations of breastfeeding for both maternal and child health outcomes, including child development and preventing noncommunicable diseases, highlights the relevance of supporting breastfeeding in high-, middle- and low-income settings.

HIV infection both directly affects the nutritional status of women and children living with HIV and indirectly affects them by altering household food security and through inappropriate choices of infant-feeding practices.

In 2016, based on revisions to the ARV drug guidelines, a greater evidence base and programmatic experience, WHO updated its guidance on HIV and infant feeding. The recommendations and good practice statements are detailed below. For guidance on what to feed infants when mothers stop breastfeeding and conditions needed to safely formula feed should this be the mother's choice, see the 2016 guidelines on HIV and infant feeding *(266).*

Implementing the following recommendations requires appropriately training and developing the capacity of health-care workers to supply them with the necessary skills and job aids and provide adequate supervision and oversight. Programmes need to be systematically monitored to ensure success and to identify and document challenges to implementation.

Clinical considerations for supporting mothers with HIV to breastfeed

Key clinical and implementation considerations for breastfeeding by mothers living with HIV while receiving ART include:

- communicating clearly and effectively the effectiveness of ART and suppressing viral loads in reducing the postnatal transmission risks through breastfeeding to health-care workers, mothers and the community;
- communicating the importance of viral load monitoring during breastfeeding to ensure that suppression is maintained;
- highlighting the value of breastfeeding for the health, development and survival of mothers living with HIV and their children when the mother is receiving and adhering to ART and has suppressed viral loads;
- implementing and sustaining specific interventions such as an integrated approach to delivering follow-up care for the mother and child as part of basic maternal, newborn and child health services (including immunization and other well-child services) to improve postpartum follow-up of mother–infant pairs and support breastfeeding practices and ART adherence;
- emphasizing postnatal prophylaxis for infants: infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP, or if they are considered at high risk, enhanced infant prophylaxis using AZT and NVP for six weeks followed by either AZT and NVP or NVP alone for an additional six weeks (see section 4.4.6); and
- linking the receipt of infant HIV testing and results with appropriate infant feeding counselling: infants living with HIV should continue breastfeeding until 24 months or longer.

For infants who acquire HIV despite interventions to prevent mother-to-child transmission, exposure to drugs through breastfeeding affects drug resistance and toxicity and may affect the success of ART regimens for the child (see section 4.8 on toxicity monitoring and drug resistance).

Implementation considerations

Investment and action to protect, promote and support breastfeeding in the general population should remain priorities of health ministries, nongovernmental organizations and other partners in all settings. HIV and maternal, newborn and child health programmes need to give priority to integrating ART services, including adherence counselling and support for infant and young child feeding, in all settings. These programmes and partner agencies need to ensure training and developing the capacity of health-care workers to implement the recommendations. Programmes and partner agencies should collect data to monitor the duration of breastfeeding by mothers living with HIV in addition to adherence to ART and the rates of retention in care of mothers and infants. Such data should be used to improve the quality of service delivery at district and local clinics.

Community and health facility approaches to support improved infant feeding practices include:

- combining group education with individual counselling sessions;
- building the skills and competencies of health-care workers to deliver infant feeding counselling;
- involving fathers and other family members;
- involving community health workers and trained health-care workers; and
- integrating programmes for preventing mother-to-child transmission of HIV with access to ART.

National authorities need to create and sustain an enabling environment that encourages appropriate feeding practices for all infants and young children while scaling up interventions to reduce HIV transmission *(266)*. As stated in the 2010 WHO guidelines on HIV and infant feeding *(267)*, health services need to support mothers living with HIV in their chosen feeding practices even when these are inconsistent with nationally recommended practices. This principle is still endorsed by WHO and remains relevant.

In all settings, implementing recommendations for mothers living with HIV should be contextualized first by the optimal infant feeding practice recommended for all mothers and infants: exclusively breastfeeding for six months and then introducing appropriate complementary foods and continuing breastfeeding for 24 months or beyond. When implementing recommendations for mothers living with HIV, national health authorities need to clearly communicate the hierarchy of what is ideal and how the recommendations for mothers living with HIV are specific to their circumstances.

Simple, consistent messaging is essential to support breastfeeding in the general population, including mothers living with HIV. Programmes should develop clear messaging that addresses views and concerns related to previous recommendations to avoid misunderstandings among health-care workers, mothers living with HIV and the general population.

In settings in which national authorities recommend replacement feeding for mothers living with HIV, similar coordinated support can probably improve the safety of replacement feeding practices. WHO and Food and Agriculture Organization of the United Nations guidance on safe preparation of powdered infant formula *(268)* provides technical information that may be helpful in the context of HIV.

Research gaps

- How does long-term postpartum exposure to low-dose ARV drugs in breast-milk affect the early and late health outcomes, especially growth, renal and bone metabolism and nervous system development, of HIV-exposed breastfeeding infants and children whose mothers are taking ART?
- In the context of HIV, what support increases exclusive and continued breastfeeding in the general population?
- How can mothers living with HIV who are receiving ARV drugs be supported to breastfeed for longer in circumstances such as returning to work or school?

6.17 Palliative care

Introduction

An essential component of comprehensive clinical management for people living with HIV is the palliative care to prevent and relieve suffering and optimize quality of life *(269)*. Common problems among people living with HIV that are managed by palliative care include pain and other physical symptoms related to HIV infection or its treatment; mood disorders and psychosocial distress related to stigmatization and poverty; and spiritual distress. Successful ART has resulted in a growing population of ageing people living with HIV, many of whom have multimorbidity, meaning that the people who need palliative care are changing. Person-centred palliative care must value people's social networks, promote quality of life and reform structurally to improve how people experience interacting with the health-care system *(270)*.

Need for palliative care among people living with HIV

Epidemiology

An estimated 12.8 million of the 38 million people living with HIV need palliative care *(271)*. This includes nearly all the 690 000 people living with HIV who died in 2019 *(272)*. The great majority of people living with HIV who would benefit from palliative care are not at the end of life but are living with HIV and its comorbidities and biopsychosocial consequences. More than 90% of the total need for palliative care among people living with HIV is in low- and middle-income countries; among children, HIV represents about 30% of worldwide palliative care need *(271)*.

Unrelieved suffering

Recent estimates of the burden of serious health-related suffering found that people living with HIV experienced almost 194 million days of serious health-related suffering *(273)*. Symptoms of health-related suffering are highly prevalent from diagnosis and persist alongside treatment, with the prevalence of anxiety (28%) and depression (34%) among people living with HIV receiving ART being higher than among people with other chronic conditions such as cancer, diabetes and multiple sclerosis *(274)*. These burdens are reflected in data showing that people living with HIV have poorer quality of life than the general population *(275)*. Among people with AIDS, 43–95% report fatigue, 82% anorexia, 30–98% pain, 41–57% nausea and vomiting, 43–62% breathlessness, 40–74% insomnia and 29–53% diarrhoea *(276)*.

Pain profoundly affects quality of life, and people living with HIV identify pain control as essential to enable a "life worth living" *(277)*. Uncontrolled symptoms have severe clinical and public health implications, including poor adherence to ART *(278)*, treatment switching *(279)*, viral rebound *(280)*, poorer quality of life *(281)*, suicidal ideation and days out of work or education *(282)*. Spiritual suffering is also burdensome among people living with HIV, especially in advanced HIV disease, when spiritual well-being can become people's primary concern *(283,284)*. Progressive illness in low- and middle-income countries places a huge mental, social, economic, physical and spiritual burden on people living with HIV and the largely female caregiving members of families *(276,285)*.

Children and young people have some symptoms and concerns in common with adults but also face specific concerns *(286)*. The palliative care needs of children and young people in sub-Saharan Africa include physical concerns (such as pain and symptom distress); psychosocial concerns (such as family and social relationships), ability to engage with age-appropriate activities (such as play and attending school); existential concerns (such as worry about death and loss of ambitions); and health-care quality (such as child- and adolescent-friendly services). Priority psychosocial concerns and health service factors vary by age *(287,288)*. It is

increasingly recognized that children living with HIV in low- and middle-income countries have multi-system chronic comorbidities despite ART *(289)*. Thus, prompt diagnosis and treatment are a priority alongside managing pain and symptoms.

Ageing and comorbidities

The successes of ART have led to improved survival and quality of life, but an increasing proportion of deaths among people living with HIV is attributable to chronic noncommunicable diseases in many settings *(290)*. By 2030, people living with HIV are estimated to be likely to have an average of three noncommunicable diseases *(291)*. A longitudinal study of mortality among people living with HIV in the United Kingdom found that only 58% of the deaths were from AIDS-defining illness, 19% cancer, 19% cardiovascular diseases, 18% infections, 12% liver disease, 6% substance misuse, 5% suicide, 5% accidents and 17% other causes (more than one option and the total therefore exceeds 100%) *(292)*. In a multisite study from Cambodia, India, Indonesia, Malaysia, Thailand and Viet Nam, 47% of deaths among adults and children with HIV were non-AIDS infections *(293)*.

Palliative care in HIV treatment

Definition of palliative care

WHO defines palliative care as the prevention and relief of suffering of adults and children and their families facing the problems associated with life-threatening illness. These problems include physical, mental, social and spiritual suffering among the people with life-threatening illness and the mental, social and spiritual suffering of family members *(294)*.

Palliative care:

- entails early identification and accurate assessment and treatment of these problems;
- enhances quality of life, promotes dignity and comfort and may also positively influence the course of illness;
- provides accompaniment for the person with life-threatening illness and family throughout the course of illness and for bereaved family members;
- should be integrated with and complement prevention, early diagnosis and treatment of HIV infection and associated conditions;
- is applicable early in the course of illness in conjunction with ART and other therapies intended to prolong life;
- is especially important near the end of life when the disease treatments may no longer be beneficial or desired by the person with life-threatening illness;
- seeks to mitigate the pathogenic effects of poverty on people with life-threatening illness and their families and to protect them from financial hardship caused by illness or disability;
- should be applied by health-care workers at all levels of health-care systems, including primary care providers, generalists and specialists in HIV or infectious disease;
- encourages active involvement by communities and community members; and
- should be accessible at all levels of health-care systems and in individuals' homes.

Palliative care is applicable from the point of diagnosis, enabling people with life-threatening illness and their families to benefit from a holistic, people-centred approach focusing on individual preferences and priorities and controlling pain and symptoms. For people living with HIV at the end of life, symptoms may worsen, priorities change and decisions about place of death and treatment withdrawal become important *(276)*.

Policy and human rights

Palliative care is recognized as a human right *(295)* and an essential component of integrated, people-centred health services. The World Health Assembly resolution on palliative care (resolution 67.19, 2014) calls for palliative care to be "integrated throughout the life-course" and recognizes it to be "fundamental to improving the quality of life, well-being, comfort and human dignity of individuals, being an effective person-centred health service" *(296)*. The most recent version of the WHO goals for universal health coverage calls for the "full spectrum of essential, quality health services, from health promotion to prevention, treatment, rehabilitation and palliative care across the life-course" *(297)*. WHO also calls for palliative care as an essential component of a comprehensive package of care for people living with HIV because of the variety of symptoms they can experience.

Although evidence consistently identifies that people with life-threatening illness prefer home death *(298–300)*, a study across 11 countries found that people living with HIV are more likely to die in a hospital than people with cancer *(301)*. Health policy should enable the preferences for care at the end of life to be honoured.

Evidence also indicates that individual members of key populations have a greater need for palliative care and worse bereavement outcomes than others *(302–304)* but may be excluded from palliative care services *(305,306)*. Access to palliative care for children lags behind that of adults, and equitable access to palliative care that reflects children's specific social, education and developmental needs is essential *(286,307)*.

Evidence for the effectiveness and cost–effectiveness of palliative care

A systematic review found that home palliative care and inpatient hospice care significantly improve outcomes in the domains of pain and symptom control, anxiety, insight and spiritual well-being *(308)*. Evidence from a randomized controlled trial of integrated palliative care for people living with HIV accessing ART in Kenya suggests that a simple intervention of brief training and using a holistic person-centred assessment tool with a proforma care plan and clinical mentorship improved quality of life, mental health, psychosocial concerns and stigma *(309–313)*.

The available evidence suggests that palliative care in low- and middle-income countries saves money for health-care systems *(314)*. Implementing a hospital-based palliative care team in a hospital in South Africa improved the proportion dying at home and reduced admissions and length of stay and costs per patient *(315)*.

Programme considerations

Essential package of care

WHO has recommended an essential package of palliative care comprising four interventions: a list of safe, effective, inexpensive, off-patent and widely available medicines; simple and inexpensive equipment; basic social supports; and the human resources needed to provide the medicines, equipment and social supports effectively and safely (Table 6.7) *(273,316,317)*.

Essential medicines

The list of medicines in the essential package of palliative care is based on the 2019 WHO Model List of Essential Medicines for palliative care for adults and children *(110,318)*. Medicines were selected based on their indispensability to prevent or relieve the most common types of suffering of people living with HIV and people with other serious illnesses, the ability of clinicians with basic palliative care training to prescribe them safely and their balance of clinical effectiveness, safety, ease of use, low cost and global market accessibility *(316,319)*. Morphine, in oral fast-release and injectable formulations, is indispensable for treating pain and refractory

terminal dyspnoea. Efforts to prevent the diversion of morphine and other controlled medicines should not result in inappropriate regulatory barriers to access to such medicines *(319,320)*. The 2020 WHO guidelines on managing chronic pain among children *(321)* also state that access to pain management is a fundamental human right, and governments must "guarantee essential medicines, which include, among others, opioid analgesics as part of their minimum core obligations under the right to health".

Non-pharmaceutical management

The availability of medicines for controlling pain and symptoms for people living with HIV is essential. In addition to pharmaceutical management, self-management may empower people living with HIV because of undertreatment stigma and challenges in accessing clinical support when pain is wrongly attributed *(277)*. A systematic review found that self-management interventions delivered online, face-to-face or group-based comprising booklets, leaflets or manuals are effective in improving the relief of pain and physical symptoms among people living with HIV *(322)*.

Clinical education

WHO recommends that all health–care providers be trained in at least basic palliative care because of the range of health-care providers who have a role in delivery, including community and primary care providers, paediatricians and HIV specialists *(313)*. Basic HIV palliative care training should aim to create competencies in assessing and relieving pain and other physical symptoms, common types of mental distress such as anxiety and depression and common types of social suffering such as stigmatization, abandonment and extreme poverty. The training also should generate competencies in empathetic and culturally sensitive communication with people with life-threatening illness, medical ethics, advance care planning, interdisciplinary teamwork, end-of-life care, bereavement support and self-care. Outlines for such curricula are available *(313,316)*.

The level of training that different types of health-care providers should require is as follows *(316)*:

- basic palliative care training (duration: 30–40 hours) for all health-care providers working at the primary care or community level who care for people living with HIV; and
- intermediate-level palliative care training (duration: 60–80 hours) for health-care professionals specializing in such fields as HIV management, infectious disease, tropical medicine, TB, oncology, haematology, family medicine, internal medicine and critical care.

Place of care

The guidance for planning palliative care services states that people living with HIV should have access to palliative care at all levels of health-care systems and in the home *(313)*. Central-level hospitals that care for people living with HIV should have a palliative care team comprising one or more doctors (ideally a palliative care specialist), nurses and a social worker or psychologist that provide inpatient and outpatient care and advice and support for clinicians providing palliative care at lower levels. District hospitals should have one or more doctors and nurses with at least basic palliative care training and a social worker who provides inpatient and outpatient palliative care as one official responsibility. In hospitals, health-care providers should initiate palliative care for people in need, relieve any type of suffering as completely as possible and create discharge plans for people returning home at the end of life to protect them from suffering. This may entail communicating with health-care providers at the community level *(313)*.

Primary health-care centres would benefit from having at least one health-care worker with at least basic palliative care training. The tasks could include initiating palliative care and planning treatment for people living with HIV with uncomplicated needs, continuing palliative

care begun in a hospital, surveillance for uncontrolled symptoms with help from community health workers, home visits when necessary and feasible, prescription refills and referral to higher levels as needed. If possible, primary health-care centres can provide inpatient hospice care for people living with HIV whose symptoms are well controlled but are unable to be cared for adequately at home. Community health workers can be taught in a few hours to recognize uncontrolled suffering among people at home, and simple valid person-centred outcome measures can enable lay community health workers to identify palliative care symptoms and concerns and communicate this information rapidly using mobile health technologies to palliative care teams *(323)*. Health-care professionals should supervise community health workers who visit people who need palliative care. Person-centred HIV care delivered in the community by trained health-care professionals can improve outcomes in all four dimensions of well-being (physical, mental, social and spiritual) and retention in care *(324)* and is a core principle of WHO's public health approach.

Social support

Social support is a basic component of the early palliative care consultation and should be accessible for anyone who needs palliative care and for their main caregiver in instances of extreme poverty *(325–327)*. Given that extreme poverty is both a cause and an effect of HIV infection, it is crucial that meaningful social support be accessible *(325)*. Such social support includes transport vouchers, cash payments, food packages and other types of in-kind support *(326,327)*. In most cases, funding for social support should come not from health-care budgets but from antipoverty or social welfare programmes. Thus, implementing all aspects of the full essential package of palliative care requires intersectoral coordination *(317)*.

6.18 Noncommunicable diseases among children and adolescents

As access to treatment improves, children and adolescents living with HIV receiving ART should have the chance to have an improved quality of life and reach their full potential. Service delivery platforms need to plan how to implement this, since screening for chronic comorbidities and disabilities, neural development and growth delays, promoting nurturing care and supporting the mental development of children and adolescents as they age are of paramount importance.

Worldwide, 530 000 children five years and younger are living with HIV, and 5.4 million children five years and younger are HIV-exposed and uninfected *(328)*.

The early years lay a foundation for health, well-being and productivity that lasts throughout childhood, adolescence and adulthood *(329)*. Failure to meet children's needs in this critical window limits their ability to achieve their full developmental potential. Children living with HIV may be especially vulnerable during this period because of the following risk factors:

- being born small for gestational age or prematurely *(330)*;
- having more severe pneumonia, diarrhoeal disease and exposure to TB *(331)*;
- receiving suboptimal breastfeeding and nutrition, resulting in poor growth;
- being cared for by a mother or other caregiver who is experiencing health challenges, both physically and mentally;
- being excluded from opportunities to interact with other children, adults and their surroundings;
- being raised in extreme poverty or exposed to violence; and

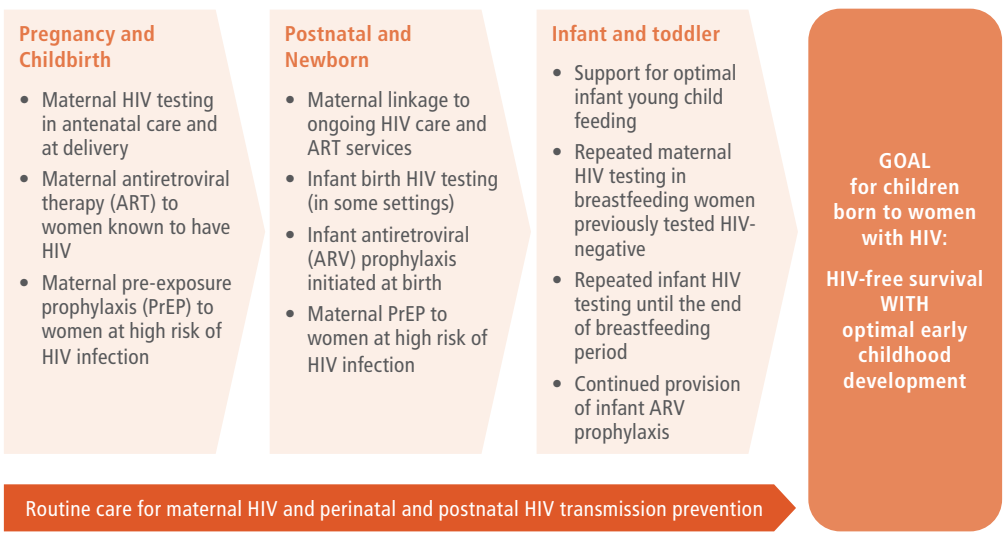
- being exposed to maternal HIV and to ARV medicine, resulting in worse developmental outcomes compared with their non-HIV-affected peers.

Enabling young children to achieve their full developmental potential is a human right and an essential requisite for sustainable development. Given the critical importance of enabling children to make the best start in life, the health sector, among other sectors, has an important role and responsibility to support nurturing care for early childhood development. WHO has produced *Improving early childhood development: WHO guideline (332)*, which provides direction for strengthening policies and programmes to better address early childhood development.

The family primarily provides the nurturing care that children need to develop in the earliest years. Many parents and other caregivers need support to put this into practice. The guideline contains four recommendations for caregivers, health professionals and other workers who can assist them as well as policy-makers and other stakeholders. The recommendations relate to (1) providing responsive care and activities for early learning during the first three years of life; (2) including responsive care and early learning as part of interventions for optimizing the nutrition of infants and young children; and (3) integrating psychosocial interventions to support maternal mental health into early childhood health and development services *(332)*.

To reach their full potential, children need the five interrelated components of nurturing care: good health, adequate nutrition, safety and security, responsive caregiving and opportunities for early learning. This begins in pregnancy and continues throughout the life-course. Adding a nurturing care lens to routine maternal, newborn and child health and HIV prevention and care services can improve the quality of the engagement between health-care workers and caregivers *(334)* (Fig. 6.3).

Fig. 6.3 Adding a nurturing care lens to maternal, newborn and child health and HIV prevention services *(334)*



Service implications

Governments and facilities need to agree on, add and monitor indicators relevant to nurturing care through routine electronic health data systems and, if possible, disaggregate data by HIV infection and exposure status *(333,334)*.

Chronic comorbidities and noncommunicable diseases

As children and adolescents age, comprehensive care remains critical. Recognition is now increasing that children living with HIV, including those taking ART, are at risk of developing chronic multisystem comorbidities and concomitant disability *(335)*. To date, HIV care has mainly focused on delivery and adherence to ART, and the burden of comorbidities associated with HIV among children is insufficiently appreciated. For adolescents, some regions have shown a shift in trend from infectious causes of hospitalization towards noncommunicable diseases *(336)*.

Common comorbidities include developmental delay and neurocognitive impairment, mental health disorders as well as certain organ system morbidities (chronic lung disease, heart disease and kidney disease) that are common among adolescents living with perinatally acquired HIV.

Growth

Although growth resumes after starting ART, children who have more profound stunting and begin ART in late childhood have a delayed growth spurt and are typically unable to reach their height potential *(337–339).* Age at initiating ART is an important predictor of bone density. In Zimbabwe, children living with HIV starting ART after the age of eight years had, on average, at least 1 standard deviation lower size-adjusted lumbar spine bone density *(340)*. This level of bone density reduction doubles the fracture risk for adults *(341)*.

Chronic comorbidities

Cardiac, renal and metabolic comorbidity has been described in adolescents with late access to suboptimal ART regimens. This should decline as less-toxic ART regimens become more widely available. However, these new regimens may require specific monitoring of other potential comorbidities, such as DTG and potential weight gain. Surveillance is crucial, including conventional growth monitoring.

Chronic lung disease

Reports of chronic lung disease associated with HIV among children mainly come from low-income settings. This difference in reporting might result from a high prevalence of risk factors in these settings, including recurrent lung infections in early life, delayed ART initiation, household air pollution, malnutrition and stunting *(342)*. Malnutrition during the first year of life might be associated with reduced lung function at one year of age, and stunting is a marker of delayed somatic growth. Stunted children could therefore have smaller lungs and reduced lung volume *(343)*.

Lung impairments and reduced lung function in childhood track through adult life, and lung injuries in childhood therefore not only prevent an individual from reaching full lung potential but also increase the risk of chronic lung disease in adult life. A study in South Africa showed a decline in lung function tracked over two years among adolescents living with HIV (9–16 years old) who were well established on ART *(344)*.

Methods for diagnosing chronic lung disease, such as spirometry and high-resolution computed tomography, are scarce in low-income settings. Chronic respiratory symptoms are therefore often empirically treated with repeated antibiotics and anti-TB therapy in settings with a high prevalence of HIV and of TB. There are no specific guidelines for chronic lung disease associated with HIV. However, preventing lung infections can mitigate the burden of chronic lung disease among children living with HIV and optimize lung health. Lung infections can be prevented by ensuring routine vaccinations (including pneumococcal conjugate vaccine and annual influenza vaccine), early ART initiation, continued co-trimoxazole prophylaxis and use

of isoniazid prophylactic therapy, avoiding exposure to tobacco smoke and indoor air pollution and optimizing nutrition.

Neurodevelopmental delay, neurocognitive disease and mental health

Children living with HIV who start ART after infancy can have subtle to severe neurocognitive deficits. A prospective study of children 5–11 years old from four countries in sub-Saharan Africa compared nervous system and mental outcomes of children living with HIV, children who had been exposed to HIV but were not infected and children who had not been exposed to HIV. The children living with HIV did worse in all cognitive domains than did the other two groups. More than 95% (239 of 246) of the children living with HIV had suppressed HIV viral load and good immune status (CD4 percentage greater than or equal to 25%), but only 1% (3 of 246) started ART in the first six months of life *(335)*.

The causes of neurocognitive impairment despite effective ART are likely to be multifactorial, including ongoing viral replication in the CNS and resulting neuroinflammation, irreversible CNS injury before ART and neurotoxic effects of ART, and could be compounded by socioeconomic and psychosocial factors *(345)*. Children with neurocognitive impairment can appear asymptomatic, with deficits missed by routine testing. Screening tools and standardized definitions that are context-specific and have been culturally validated are scarce. However, a study in South Africa in 2019 validated a an international HIV dementia screening tool for young people *(346)*.

Several studies report a high prevalence of mental health disorders among children and adolescents living with HIV. A large study in Uganda *(347)* recruited more than 1300 children and adolescents living with HIV reported a 17.% (233 of 1339) prevalence of any mental health disorder and a 10% (128 of 1339) prevalence of any behavioural disorder, most commonly attention-deficit/hyperactivity disorder. These disorders were more common among adolescents than among children and commonly occurred concurrently with each other. Similarly, a study in South Africa *(348)* reported that adolescents living with HIV had poorer functional competence, self-concept and motivation and higher levels of depression, disruptive behaviour, attention-deficit/hyperactivity disorder symptoms and clinically significant anger compared with their HIV-negative peers. Children living with HIV face recurrent and cumulative psychosocial stressors that differ from other chronic childhood illnesses, such as stigma and discrimination, responsibility for the welfare of siblings or other family members who are ill, illness and the death of their parents and unstable guardianship. These stressors can hamper development of protective mechanisms and leave children mentally vulnerable and ill equipped for coping with challenges, most likely increasing the risk of mental health disorders. Mental health disorders affect an individual's adherence to ART and are associated with impaired quality of life but typically receive little attention compared with physical health concerns.

Up to half of adult mental health problems begin during childhood and adolescence *(349)*. This highlights the necessity to implement screening during adolescence. Promoting mental health and preventing mental health disorders and problems are being increasingly emphasized, with opportunities to integrate psychosocial support and mental health at key points, such as at the time HIV status is disclosed.

Cancer

Children living with HIV with advanced immunosuppression before initiating ART or who started ART at an older age have an increased risk of cancer compared with those with modest immunosuppression or who began ART in infancy *(350)*. Linked data from five ART programmes for children and four paediatric oncology units in South Africa showed an overall incidence of cancer of 82 per 100 000 person-years. The most common types were Kaposi's sarcoma, with

an incidence of 34 per 100 000 person-years, and non-Hodgkin lymphoma, with an incidence of 31 per 100 000 person-years *(351)*.

A study from the United States of America, which followed up children for 10 years, showed that, although the incidence of Kaposi's sarcoma and non-Hodgkin lymphoma declined in the ART era, the risk of developing non-AIDS-defining cancer did not *(352)*. This increased risk of non-AIDS-defining cancer highlights the need for continued monitoring of children growing up with HIV.

Multimorbidity

In a study in South Africa *(353)*, more adults living with HIV receiving ART had multimorbidity in the younger age groups (18–35 and 36–45 years old) than in an older age group (46–55 years old), with 26% of 18- to 35-year-olds and 30% of 36- to 45-year olds having multimorbidity. Since the risk factors for multimorbidity include time on ART, adolescents living with perinatally acquired HIV may be at increased risk as they progress through their life-course. Adolescents in resource-limited settings may be specifically vulnerable because of a lack of primary prevention of common noncommunicable diseases and a high burden of inflammatory coinfections.

Service delivery

Various service delivery platforms already established could be used to screen for and manage noncommunicable diseases among children at different stages of their lives. For children younger than five years, examples include early childhood development, under-five clinics and HIV services. For children 5–9 years old, examples include integrated school and HIV services. For adolescents 10–19 years old, examples include adolescent-friendly services. Although implementing screening and prevention of noncommunicable diseases or comorbidities presents many challenges, opportunities to integrate this kind of care into existing adolescent activities are numerous. Some clinics have already established adolescent groups to address various health issues *(354)*. HIV is one of the only conditions that results in an adolescent population interacting regularly with the health system. This should be leveraged to integrate a more comprehensive approach to health. Table 6.7 summarizes the platforms, screening approaches, tools needed and interventions that are applicable across young children, children of school age and adolescents.

Comprehensive HIV care for children and adolescents includes:

- earlier initiation of ART to prevent complications:
- monitoring growth and musculoskeletal and neurocognitive development;
- screening for heart, lung, kidney and neurocognitive disease;
- assessing psychosocial status (schooling and guardianship) and mental health;
- managing common mental health disorders and providing psychosocial support;
- optimizing nutrition;
- catching up or revaccinating according to WHO guidelines, such as pneumococcal and influenza vaccination;
- HPV vaccination for adolescents;
- cervical cancer screening after sexual debut;
- referring to clinical specialties for management if feasible;

- liaising with disability and rehabilitation services;
- school-based programmes to provide educational support;
- leveraging existing early child development platforms for supporting children living with HIV; and
- linking to community-based psychosocial support services.

Table 6.7 Service Delivery: Potential ways to integrate screening and possible interventions

	Children 0-5	5-10 years school age	Adolescents 10-19 years
Platform	Mother and child services	School based/ HIV clinics	School based services/ HIV services
Screen	Anthropometry, neurodevelopmental screening including hearing and vision, urine for renal disease	Weight, height, urine dipstick, hearing, vision, symptoms of depression, neurocognitive problems	Weight, height, urine dipstick, Blood pressure, glucose, symptoms of depression, neurocognitive problems, substance abuse
Tools	"Ten Questions"[a], urine dipstick for sugars and protein	"Ten Questions", urine dipstick for sugars and protein	y-IHDS[b], urine dipstick for sugars and protein
Intervention	Referral for hearing assessment, early detection of renal disease, nutritional interventions, nurturing care framework	Referral for hearing testing, early detection of renal disease, nutritional interventions, mental health interventions	Implement HAT[c] guidelines, provide care for diabetes and hypertension Health education: healthy diet and exercise

[a] Ten questions-Ten Questions (TQ) screen, a standardized medical history and physical examination conducted by a medical doctor, with hearing and vision screening, psychological assessment for cognition and language delay, and voluntary HIV testing.

[b] y-IHDS (youth international HIV dementia scale)

[c] HAT- Helping Adolescents Thrive (Guidelines on promotive and preventive mental health interventions for adolescents)

Research priorities

The epidemiology and clinical spectrum of noncommunicable diseases among children and adolescents living with HIV and the pathogenesis of these issues need further study. Standard definitions of comorbidities based on population-specific normative ranges are needed. Optimum screening, when to start screening and management strategies are not well defined and need further study. Validated age-appropriate and culturally appropriate screening tools specifically for mental health and neurocognitive disease are needed. Further research on interventions for prevention and treatment are needed, including antibiotics, antiviral agents, anti-inflammatory drugs and vitamin D as well as feasible and effective educational and mental health interventions. How the ARV drugs used for prevention and treatment interact among children needs to be studied.

Additional resources relating to Chapter 6

Comprehensive cervical cancer control: a guide to essential practice. 2nd ed. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/144785).

WHO guidelines for treatment of cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ: cryotherapy, large loop excision of the transformation zone, and cold knife conization. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/104174).

Human papillomavirus vaccines: WHO position paper, May 2017. Wkly Epidemiol Rec. 2017;92:241–268 (https://apps.who.int/iris/handle/10665/255354).

WHO guidance note: comprehensive cervical cancer prevention and control: a healthier future for girls and women. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/78128).

Use of cryotherapy for cervical intraepithelial neoplasia: evidence base. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/handle/10665/70855).

Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/44260).

Prevention and control of noncommunicable diseases: guidelines for primary health care in low-resource settings. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/76173).

Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations, 2016 update. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/246200).

WHO, UNODC, UNAIDS. WHO, UNODC and UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/44068).

Community management of opioid overdose. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/handle/10665/137462).

Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization; 2009 (https://apps.who.int/iris/handle/10665/43948).

Guidance on prevention of viral hepatitis B and C among people who inject drugs. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/75357).

Integrating collaborative TB and HIV services within a comprehensive package of care for people who inject drugs: consolidated guidelines. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/204484).

HIV prevention, treatment, care and support for people who use stimulant drugs. Vienna: United Nations Office on Drugs and Crime; 2019 (https://www.unodc.org/documents/hiv- aids/publications/People_who_use_drugs/19-04568_HIV_Prevention_Guide_ebook.pdf).

Guidelines for the management of symptomatic sexually transmitted infections. Geneva: World Health Organization; in press.

WHO guidelines for the treatment of *Neisseria gonorrhoeae*. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/246114).

WHO guidelines for the treatment of *Chlamydia trachomatis*. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/246165).

WHO guidelines for the treatment of *Treponema pallidum* (syphilis). Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/249572).

WHO guidelines for the treatment of genital herpes simplex virus. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/250693).

WHO guidelines on syphilis screening and treatment for pregnant women. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259003).

Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with men and transgender people: recommendations for a public health approach. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44619/9789241501750_eng.pdf).

Prevention and treatment of HIV and other sexually transmitted infections for sex workers in low- and middle-income countries: recommendations for a public health approach. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/77745).

Consolidated guidelines on HIV testing services, 2019. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/336323).

Dual HIV/syphilis rapid diagnostic tests can be used as the first test in antenatal care: policy brief. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/329965).

Brief sexuality-related communication: recommendations for a public health approach. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/170251).

Violence against women

Responding to children and adolescents who have been sexually abused: WHO clinical guidelines. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259270).

Strengthening health systems to respond to women subjected to intimate partner violence or sexual violence: a manual for health managers. Geneva: World Health Organization; 2015 (https://apps.who.int/iris/handle/10665/259489).

Responding to intimate partner violence and sexual violence against women: WHO clinical and policy guidelines. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/85240).

Sexual and reproductive health guidelines for women living with HIV

WHO, UNFPA. Sexual and reproductive health of women living with HIV/AIDS. Guidelines on care, treatment and support for women living with HIV/AIDS and their children in resource-constrained settings. Geneva: World Health Organization; 2006 (https://apps.who.int/iris/handle/10665/43473).

Consolidated guideline on sexual and reproductive health and rights of women living with HIV. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/254885).

Nutrition and HIV

Essential nutrition actions: mainstreaming nutrition through the life-course. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/32626).

HIV and infant feeding in emergencies: operational guidance: the duration of breastfeeding and support from health services to improve feeding practices among mothers living with HIV. Geneva: World Health Organization; 2018 (https://apps.who.int/iris/handle/10665/272862).

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5. IMAI district clinician manual: hospital care for adolescents and adults – guidelines for the management of illnesses with limited resources. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/handle/10665/77751, accessed 1 June 2021).
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7. SERVICE DELIVERY

7.1 Introduction

WHO's public health approach to delivering ART has enabled access to treatment and care for people living with HIV to be scaled up, with an estimated 67% of people living with HIV receiving ART in 2020 – 25.4 million of 38 million people living with HIV, up from 7.8 million in 2010 *(1)*.

To reinforce the delivery of ART at scale, WHO promotes a public health approach to ART, using simplified and standardized ART that supports the decentralization of care, task sharing and community delivery and more efficient procurement and supply management *(2)*. The 2016 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(3)* included a chapter that provides several recommendations for delivering HIV services across the cascade of care from HIV testing to long-term viral suppression.

Notwithstanding the progress made in increasing access to treatment, challenges remain. Studies over the past decade have found that many people living with HIV disengage from care after starting treatment. In sub-Saharan Africa, about one third of adults disengaged from care within five years of starting treatment *(4)*. Long-term retention in care is an important challenge across geographical settings and age groups *(5–8)*, and those who have disengaged and stopped taking ART are at increased risk of transmitting HIV to other people, progressing to AIDS and dying.

This chapter provides updated recommendations and good practice statements in the following areas:

- linkage from HIV testing to enrolment in care;
- differentiated service delivery;
- people-centred care;
- initiating ART outside the health facility;
- rapid initiation of ART, including same-day start;
- adherence:
  - monitoring adherence to ART in routine programme and care settings;
- retention in care;
- tracing and re-engagement in care;
- frequency of clinical visits and ART pick-up;
- task sharing:
  - task sharing for initiation and maintenance of ART;
  - task sharing of specimen collection and point-of-care testing;
- decentralization;
- integrating and linking services:
  - delivering ART in maternal and child health care settings;
  - delivering ART in TB treatment settings and TB treatment in HIV care settings;

  - integrating sexual and reproductive health services, including contraception, within HIV services;
  - integrating diabetes and hypertension care with HIV care;
  - ART in settings providing opioid substitution therapy;
  - diagnostic integration;
- care transition;
- delivering high-quality HIV services to adolescents; and
- psychosocial interventions for adolescents and young adults living with HIV

Special considerations for the continuity and quality of service delivery:

- quality service delivery;
- ensuring a stable supply chain of ARV drugs; and
- laboratory and diagnostic services and connectivity.

Applicability of service delivery recommendations

In contrast to most clinical interventions, service delivery interventions are generally highly context specific in terms of both relative effectiveness and relative importance in a given context. Consistent with the burden of disease, much of the evidence supporting the recommendations in this chapter comes from studies undertaken in sub-Saharan Africa. Recognizing the importance of streamlined, standardized approaches to scaling up HIV services in settings with limited resources, the public health approach emphasizes strategies such as task sharing, decentralization and integrating HIV services with other public health programmes and patient and community empowerment. High-income countries with more resources and fewer HIV cases favour a more individualized approach to HIV care, although the overarching framework of the public health approach provides the setting within which this more personalized service delivery can occur.

Importantly, several populations are subject to structural barriers, including stigma, discrimination, criminalization and violence. This is especially important for women, young girls and adolescents and key populations, who are subject to these barriers across the HIV care cascade. Although service delivery is primarily aimed at developing programmatic guidance to help implement all the WHO recommendations, the basic principles for developing these WHO recommendations align with the concept of people-centred care, the public health approach and a rights-based approach.

The forthcoming WHO consolidated guidelines on HIV services for key populations describe essential strategies for an enabling environment, which include developing supportive legislation, policy, including working towards decriminalizing behaviour, financial commitment, addressing stigma and discrimination, empowering communities and addressing violence against key populations. WHO also supports a strong emphasis on workforce training against stigma, discrimination and strategies to support those that are subject to violence, to ensure that all populations benefit from accessing better and safer health-care services.

7.2 Linkage from HIV testing to enrolment in care

Recommendation (2016)

Following an HIV diagnosis, a package of support interventions should be offered to ensure timely linkage to care for all people living with HIV *(strong recommendation, moderate-certainty evidence)*.

The following interventions have demonstrated benefit in improving linkage to care following an HIV diagnosis:

- **streamlined interventions to reduce time between diagnosis and engagement in care, including (1) enhanced linkage with case management; (2) support for HIV disclosure; (3) tracing; (4) training staff to provide multiple services, and (5) streamlined services** *(moderate-certainty evidence)*;
- **Peer support[a] and navigation approaches for linkage** *(moderate-certainty evidence)*; **and**
- **quality improvement approaches using data to improve linkage** *(low-certainty evidence)*.

[a] Includes peer counselling.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infections: recommendations for a public health approach – second edition (3)*

Good practice statements (2019)

ART initiation should follow the overarching principles of providing people-centred care. People-centred care should be focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations. It should promote the engagement and support of people and families to play an active role in their own care through informed decision-making.

All people newly diagnosed with HIV should be retested to verify their HIV status before starting ART, using the same testing strategy and algorithm as the initial test. To minimize the risk of misdiagnosis, this approach should be maintained in settings in which rapid ART initiation is being implemented.

The introduction of the "treat all" recommendation (ART for all people living with HIV regardless of CD4 cell count) supports the rapid initiation of ART, including the offer of same-day initiation where there is no clinical contraindication.

People with no contraindication to rapid ART initiation should be fully informed of the benefits of ART and offered rapid ART initiation, including the option of same-day initiation. Rapid start of ART is especially important for people with very low CD4 cell counts, among whom the risk of death is high. People should not be coerced to start immediately and should be supported in making an informed choice regarding when to start ART.

Source: *Consolidated guidelines on HIV testing services, 2019 (9)*

Background

Linkage to prevention, treatment and care following HIV testing is a major global challenge. Improvements in treatment availability have enabled higher rates of linkage *(10)*. Despite this progress, important gaps remain, especially for key populations, men, young people and people living with HIV who had been previously diagnosed and had not initiated ART or who had started treatment but had disengaged or been lost to follow-up. Many men remain untested, and those with HIV continue to be diagnosed and linked to treatment and care late: in many settings, men have a higher HIV mortality rate than women *(11)*. For infants who are tested, delays in obtaining results and further losses in the treatment cascade still occur. As a result, less than one third of perinatally infected infants are linked to services and initiate ART in a timely manner *(12)*. Across regions, significant linkage to care disparities exists. Eastern and southern Africa has the largest absolute gap, and eastern Europe and central Asia have the lowest proportions of people who know their HIV status receiving ART.

Linkage to HIV treatment, prevention, care, support and other relevant services is the primary responsibility of HIV testing services and the testers and providers delivering HIV testing services *(9)*. Multiple factors may hinder successful linkage to care, including distance from services, transport costs, long waiting times at the facility and, for those testing positive, stigma and disclosure-related concerns. As programmes expand access to HIV testing services, linkage to HIV care should be improved through interventions that support people in the initial steps in the continuum of care. Such interventions may vary based on the local context, including the health-care delivery systems, geography and target population. A combination of interventions is needed to improve linkage to prevention, care and treatment for specific groups at risk, especially for key populations and men.

Post-test counselling messages remain key. They should be concise, addressing the needs of the client and focusing on supporting linkage to care. Post-test counselling messages need to be tailored to specific populations and their situations and whether their test results are HIV-positive, negative or inconclusive or they already know their status and need to engage or re-engage in care. Messages need to provide clients with the latest information, including:

- the personal health benefits of early ART;
- that people living with HIV receiving ART who achieve and maintain viral suppression cannot transmit HIV to their partners; and
- the benefits of voluntary provider-assisted referral for people living with HIV.

All people with HIV-positive diagnoses should be offered a package of support interventions that ensure timely linkage to care. WHO recommends co-located and well-coordinated ART services and peer support and peer navigation to facilitate linkage. Several other approaches can be considered among specific groups with low linkage rates – such as men, young people and key populations. These approaches could include ART initiation outside the health facility, friendly and flexible services designed to suit these groups and digital platforms such as linkage support via social media and videos.

People who are HIV-negative but at ongoing risk also need to be linked to effective prevention. Post-test counselling messages should include information on HIV prevention interventions and how to access them, such as male and female condoms, PrEP methods, voluntary medical male circumcision for men and boys in eastern and southern Africa and harm-reduction services for people who inject drugs. Once these people are engaged in prevention services, HIV testing services will continue to be part of prevention monitoring – such as regular testing among people taking PrEP – to identify people newly infected so that they can start ART as soon as possible.

For more information on post-test services and linkage to care, see *Consolidated guidelines on HIV testing services for a changing epidemic (13)* and Chapter 4 in *Consolidated guidelines on HIV testing services, 2019 (9)*.

WHO's five Cs

The five Cs are principles that apply to all HIV testing services and in all circumstances: consent, confidentiality, counselling, correct and connection.

The last C – connection – states that linkage to prevention, care and treatment services should include the provision of effective and appropriate follow-up as indicated, including long-term prevention and treatment support. Providing HIV testing services where there is no access or poor linkage to care, including ART, has limited benefit for people living with HIV. The providers and testers delivering HIV testing services are responsible for linkage.

Rationale and supporting evidence

The recommendations made in 2016 were supported by a systematic review *(3)* that identified three main areas of intervention: (1) streamlined services; (2) peer support and navigation and (3) quality improvement approaches.

Streamlined services

The review showed that multifaceted interventions to reduce time between diagnoses and engagement in care and ART initiation were associated with increased rates of ART initiation, including (1) enhanced linkage with case management, (2) support for HIV disclosure, (3) patient tracing for those who failed to engage in care, (4) training staff to provide multiple services and (5) streamlined services to accelerate the time to initiation. Multifaceted, streamlined services may use incentives to improve linkage to care and ART initiation.

Peer support and navigation

The specific interventions evaluated included home visits, peer support, including for navigating the health-care system, and enhanced counselling. The evidence for peer support and navigation interventions was overall of moderate certainty, due either to observational study design or the small number of trials identified. In the reviewed studies, peer navigators assisted people to link from community-based testing services to health-care settings where HIV care is provided.

Quality improvement

Quality improvement interventions have shown benefits for linkage to care, especially for programmes to prevent the mother-to-child transmission of HIV *(14)*. Integrated service delivery – providing ART in TB and maternal, newborn and child health care settings – has been found to reduce time between diagnosis and ART initiation. A qualitative evidence synthesis found that people's experience of positive interaction with their health-care providers supports linkage to HIV care *(15)*. Disclosure support also positively affected linkage.

Cost and cost–effectiveness

Costs vary depending on the selected intervention and implementation context. Effective linkage to HIV care following an HIV diagnosis potentially improves programme effectiveness, supports earlier ART initiation and reduces loss to follow-up before treatment initiation. None of the studies reported estimates of the cost or cost–effectiveness of support interventions.

Equity and acceptability

A qualitative evidence synthesis identified 25 studies of single and combined interventions to support linkage to care *(15)*. Key areas of convergence included counselling and support interventions that (1) highlight the importance of positive interactions with health-care workers or case managers (high certainty), and (2) family and peer support (moderate certainty). For service delivery interventions, (1) process and discussion of the implementation of interventions (high certainty) and (2) task sharing interventions (high certainty) were all acceptable to improved linkage. HIV programmes need to address barriers to linkage to HIV care and ART initiation. This is especially important for populations that face multiple barriers, both structural and individual, in accessing HIV services.

Feasibility

Several of the interventions are effective in improving linkage and are being implemented in different settings, including use of peer support, which has been found to provide benefits across multiple points in the cascade.

Implementation and population considerations

Pregnant and breastfeeding women

Testing during pregnancy is usually conducted in antenatal care and – unless treatment is also provided at the same location – there is often a high rate of disengagement from care since mothers and health-care workers may be more focused on pregnancy care. Solutions include:

- integrating HIV and maternal, newborn and child health services, so that testing and treatment are provided in one place; and
- if integration is not appropriate, such as in low-prevalence settings, using peer support systems to ensure linkage between antenatal care and ART care service may be valuable.

Optimal maternal retesting time points must be considered during pregnancy and postpartum. In settings with a high burden of HIV infection, retesting is advised for all pregnant women with an unknown or HIV-negative status during late pregnancy (third trimester). Catch-up testing is needed if the first test or retest is missed or delayed. Countries with a high burden of HIV infection could consider an additional retest in the postpartum period for specific districts or regions with a high HIV burden or incidence, for women from key populations and women who have a partner living with HIV who does not have suppressed viral loads *(9)*.

Children

There is historically poor retention among children, especially for infants tested using early infant diagnosis within programmes to prevent the mother-to-child transmission of HIV. Solutions include:

- using point-of-care early infant diagnosis to improve linkage;
- using SMS, GSM or GPRS printers to speed up the return of results from central laboratories; and
- using family-centred care service delivery models, in which the mother, her baby and her partner receive care at the same point of care.

Adolescents

Developmental changes during adolescence may mean that not all adolescents have the ability to cope with an HIV diagnosis. Adolescents may also have limited awareness of their own health needs and of the availability of services as well as limited experience and confidence in navigating health services. Consent requirements may restrict access to treatment and care. Solutions include providing adolescent friendly linkage services; mechanisms involving outreach to adolescents such as peer-based interventions; community-based services; other outreach services; support groups; mobile technology, social media or call centres. These linkage mechanisms should be introduced at the point of testing.

Key populations

Key populations have been defined as people who are at increased risk because of specific behaviour compounded by structural challenges such as criminalization, violence and stigma and discrimination which affect their access to health services. For HIV, key populations include men who have sex with men, sex workers, transgender people, people in prison and other closed settings and people who use or inject drugs.

Although the health interventions for key populations do not differ from those of other people at risk of or living with HIV, their access is often compromised and delivery of services may therefore need to be adapted. Involving key populations in designing, implementing and providing services is critical to ensure that the services are offered in a way that they can actually access them.

Community-based service delivery, including through peers, has shown to be more effective in many settings, especially where laws criminalize same-gender sex, sex work or drug use.

Particular issues are relevant for people in prisons and other closed settings. Not only access to high-quality health services when imprisoned as a matter of equity but also because of the major risk of treatment interruptions when transitioning between (and within) prisons and the community. Implementing safety measures to ensure the continuity of care is critical, such as providing several months of treatment to people who move back into the community to address issues of housing, health insurance, health-care provider, etc.

Additional evidence-informed implementation strategies *(9)*

In contexts, settings and populations with suboptimal linkage, the following additional evidence-informed implementation strategies can be considered:

- peer and community support and follow-up, including patient navigators and linkage escorts;
- home-based ART initiation and care;
- incentives, including financial incentives;
- friendly and flexible services;
- new digital platforms; and
- (re)linking people to treatment and care.

These may be especially useful for supporting the scale-up of self-testing and community-based HIV testing services, most notably home-based and outreach models which could have low linkage rates.

Countries should review their national guidelines and consider including a clear linkage strategy and policy, including specific approaches, interventions and designation of cadres supporting linkage and rapid ART initiation, and monitoring effectiveness. Policies need to support HIV testing services sites and testing providers to support linkage to care, including linking patient unique identifiers and revising HIV testing services registries to include evidence of linkage.

Research gaps

Evaluation of strategies aimed at improving linkage to care are needed to build a stronger evidence base. Future studies should disaggregate effects by gender, key population and age. Costing studies and cost–effectiveness analysis are needed to better inform policy decisions.

Further research is needed on whether and how digital media platforms, especially social media and web-based tools, can be adapted to facilitate linkage and rapid ART initiation at an affordable price. Further research is also needed on strategies to support people living with HIV who already know their status and link them back into care after they decline ART or being lost to follow-up.

In addition, more evidence is required on the feasibility, effectiveness and cost–effectiveness of strategies to link people living with HIV and their sexual or social networks (who have recent or ongoing HIV risk) to HIV prevention services.

7.3 Differentiated service delivery for HIV treatment

In nearly all countries, HIV treatment was delivered in the initial phase of rapid scale-up based on a one-size-fits-all, clinic-based model largely undifferentiated for individual needs *(16)*. As national guidelines have evolved towards comprehensive care, prevention, earlier diagnosis and initiating ART for all people living with HIV, differentiated service delivery for HIV treatment has become a critical component of recognizing the diversity of needs of people living with HIV. Differentiated service delivery, previously referred to as differentiated care, is a person-centred approach that simplifies and adapts HIV services across the cascade in ways that both serve the needs of people living with and vulnerable to HIV and optimize available resources in health systems *(17)*. The principles of differentiated service delivery can be applied to prevention, testing, linkage to care, ART initiation and follow-up and integration of HIV care and coinfections and comorbidities. This section focuses on differentiated service delivery for HIV treatment (see Chapter 2 for service delivery approaches for testing).

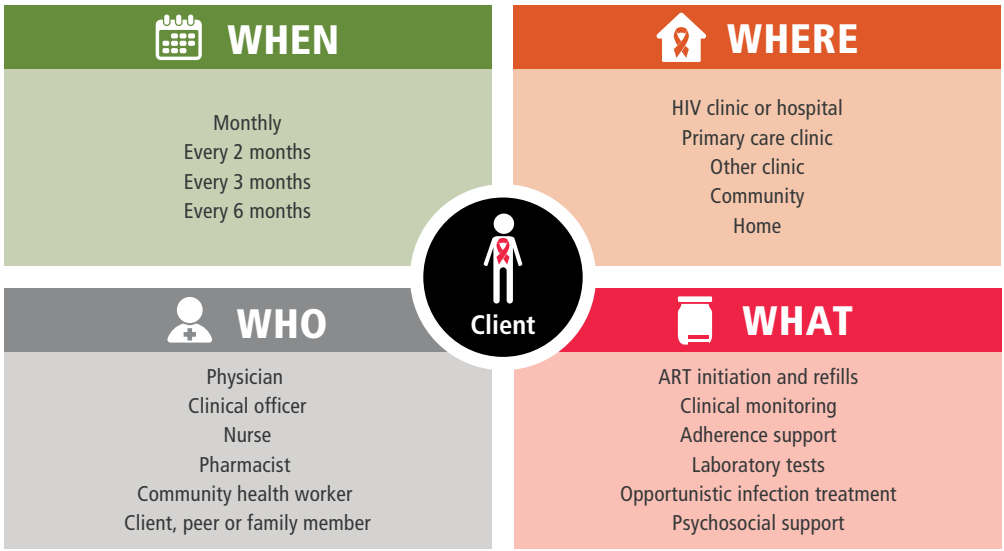
As national guidelines have evolved towards initiating ART for all people living with HIV regardless of clinical and immune status, HIV programmes have been challenged to manage an increasingly diverse set of people's needs. The 2016 WHO consolidated HIV treatment guidelines *(3)* identified four groups of people with specific clinical needs: individuals presenting or returning to care with advanced HIV disease; individuals presenting or returning to care when clinically well; individuals established on ART; and individuals receiving an ART regimen that is failing *(18)*. Differentiated service delivery for HIV treatment has focused primarily on people who are clinically stable (established on ART – see Box 7.1). Subsequently, the need has been recognized to adapt services for those with advanced HIV disease, high viral load and comorbidities through simplified care packages and differentiated models of service delivery; the principles of differentiating service delivery according to the needs of different groups has also been extended to improving the uptake of HIV testing and prevention.

In addition to considering people's clinical needs, differentiated service delivery for HIV treatment should also consider the specific populations and contextual settings. For example, differentiated service delivery models should be designed to address the needs of children and adolescents, pregnant and breastfeeding women and key populations. There is also increasing experience of how such models have been adapted in settings with lower HIV prevalence, acute conflict or other emergency responses *(19)*.

Differentiated service delivery for HIV treatment is based on four building blocks (Fig. 7.1). In any given differentiated service delivery model for HIV treatment, the building blocks need to be defined separately for clinical consultations, ART refills and psychosocial support.

Since 2016, several countries have adopted and scaled up differentiated service delivery as part

Fig. 7.1 The building blocks of differentiated service delivery for HIV treatment



of national policy, especially in sub-Saharan Africa and for adults established on ART *(20)*. The definition of being established on ART (stability) should be applied to all populations, including those receiving second- and third-line regimens, those with controlled comorbidities, children, adolescents, pregnant and breastfeeding women and key populations. These populations often represent specific cohorts in which retention and suppression of viral loads has been challenging and hence may benefit more from differentiated service delivery for HIV treatment models adapted to their needs *(21)*.

Box 7.1 Criteria for determining whether a person is established on ART

To support the implementation of these recommendations, WHO has developed criteria for determining whether a person has been successfully established on ART:

- receiving ART for at least six months;
- no current illness, which does not include well-controlled chronic health conditions;
- good understanding of lifelong adherence: adequate adherence counselling provided; and
- evidence of treatment success: at least one suppressed viral load result within the past six months (if viral load is not available: CD4 count >200 cells/mm^3 (CD4 count >350 cells/mm^3 for children 3-5 years old) or weight gain, absence of symptoms and concurrent infections).

The provision of ART should not depend on receiving other services. Differentiated service delivery for HIV treatment aims to enable clinical consultations to be carried out separately from other visits such as visits for ART refills and/or, if appropriate, psychosocial support. As outlined above, the building blocks for clinical consultations may differ from those for ART refills or psychosocial support. Psychosocial support may be aligned with clinical consultation and ART refill visits or may be provided separately through additional community and peer support systems. Multi-month refills and dispensing may be used alone or within any of the four categories of differentiated service delivery for HIV treatment listed below, each of which provides additional benefits to both the health system and clients. Multi-month refills may also be used for children older than two years, since dosage is adjusted less frequently beyond that age *(21)*. The recommendations on the frequency of clinical visits and ART refills are outlined in Chapter 5 *(21)*.

Differentiated service delivery models for HIV treatment described in practice and the literature can be described within four categories:

- group models managed by health-care workers;
- group models managed by clients;
- individual models based at facilities; and
- individual models not based at facilities.

The most common example of a group managed by health-care workers is the ART adherence club. In a South African study including 3216 people across a large urban district, adherence club retention was 95% at 12 months and 89% at 24 months *(22)*. Most recipients of care remained in care (87%) and had suppressed viral loads (94%) up to three years after entering an adherence club, with attendance highly protective against disengagement *(23,24)* compared with conventional care. Adherence club members receiving six-monthly ART refills had similar 24-month retention (93% versus 94%), higher viral load completion (94% versus 89%) and similar viral load suppression (96% versus 98%) versus those who received standard care (two-monthly refills and then four months at the end of the year) *(25)*. In Zambia, rates of late drug pick-up are lower among participants in urban adherence clubs than among clinic-based participants. This model has also been demonstrated to be acceptable to both health-care workers and clients *(26)* and cost-effective *(27)*. Positive outcomes of groups managed by health-care workers in terms of improved retention and viral suppression have also been reported across populations, including adolescents *(28)*, children and their caregivers *(29)*, postnatal women *(30)*, men who have sex with men *(31)* and for those who have previously struggled with adherence, demonstrating the benefits of such a group approach to achieve and maintain viral suppression among people with previous non-suppressed viral loads *(32)*.

Groups managed by clients meet at an agreed community location and nominate a member to collect ART for the group on a rotating basis. Common examples include community adherence groups, community ART refill groups and community client-led ART delivery. Data from client-managed group models have shown improved retention across a range of settings in sub-Saharan Africa *(33–35)*. Qualitative evidence supports reduced costs, especially from the client perspective, and increased time savings and benefits from the peer support available within this group model *(27,36–39)*. Health-care workers favoured client-managed groups because they can decongest the clinics and reduce workload *(40,41)*. Client-managed groups have also been implemented for family groups, key populations *(40)* and in unstable settings to support adherence *(37,42,43)*.

Individual models based at facilities are commonly known as fast-track or quick pick-up and go beyond extending the ART refill duration. Assigning a specific place (such as direct pick-up from a pharmacy) and time for ART refills that does not involve consultation with a health-care worker for clinical review or scripting minimizes time spent at the clinic. Evidence from such fast-track models has demonstrated reduced waiting times *(44,45)*, reduced missed appointments *(46)* and reduced costs from a limited societal and health ministry perspective *(47)*. A positive impact on retention and suppression of viral loads has also been documented. In Malawi, retention at five years after enrolment in a six-monthly appointment fast-track model was >86% versus 47% among those who were eligible but did not enrol *(48)*. In Zambia, those in the fast-track model were more likely to be retained at 12 months (relative risk (RR) = 1.52) and maintain viral suppression (RR = 1.07) *(49)*. The benefits of this approach have also been demonstrated in low-prevalence *(50)* and politically unstable settings *(43)* and for children *(51,52)*. A study of extended ART refills for more than 22 000 children across six sub-Saharan African countries found that 66% had their ART refills extended beyond one month. Of those with extended refills, only 2.6% were lost to follow-up and 2% died; suppression of viral loads remained high over five years, ranging by year from 79% to 85% *(51)*.

Individual models outside facilities vary according to where in the community services are provided and by whom. They can be divided into fixed community points (including private or community pharmacies), mobile outreach ART delivery and home delivery. High retention has been reported from several countries, including the Democratic Republic of the Congo, South Africa, Uganda and Zambia *(53–56)*. In the Democratic Republic of the Congo, ART refills are provided from community sites run by treatment-literate peers. Fixed community ART delivery points have also provided six-month ART refills *(34)* and been implemented for children *(57)* and key populations via drop-in centres *(58)*. Home delivery of ART has been studied in Kenya, South Africa and Uganda, with mixed results on retention and mortality *(59,60)*. In settings in which costs were analysed, health service and patient costs were lower for home delivery than for facility care *(61)*. The relevance of home delivery within the model mix is context specific in relation to feasibility for the health system and factors such as distance and stigma. Less published evidence is available for mobile outreach approaches, but this approach does have the potential to support an integrated approach to the community delivery of other health services.

A recent rapid systematic review of literature documenting the outcomes of differentiated service delivery for HIV treatment *(59)* included 29 publications. Of the 37 models described, seven (19%) were facility-based individual models, 12 (32%) individual models based outside facilities, five (14%) groups led by clients and 13 (35%) groups led by health-care workers. When a comparison with conventional care was provided, retention in most differentiated service delivery models was within 5 percentage points of that for conventional care; when no comparison was provided, retention generally exceeded 80%. For suppression of viral loads, all those with a comparison to conventional care reported a small increase in suppression in the differentiated service delivery model; reported suppression exceeded 90% in 11 of 21 models *(62)*.

A review of the available literature suggests that differentiated service delivery for HIV treatment for those who are established on ART saved patients substantial money on travel costs and greatly reduced the time required to receive ART, including time spent on transport, waiting in the queue or having a clinic visit, and modestly reduced the resources the health system used *(27)*.

7.4 People-centred care

Good practice statement (2021)

Health systems should invest in people-centred practices and communication, including ongoing training, mentoring, supportive supervision and monitoring health-care workers, to improve the relationships between patients and health-care providers.

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Good practice statements (2016)

HIV programmes should:

- **provide people-centred care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and engage and support people and families to play an active role in their own care by informed decision-making;**
- **offer safe, acceptable and appropriate clinical and non-clinical services in a timely fashion, aiming to reduce morbidity and mortality associated with HIV infection and to improve health outcomes and quality of life in general; and**
- **promote the efficient and effective use of resources.**

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

Background and rationale

People-centred health services are an approach to care that consciously adopts the perspectives of individuals, families and communities and sees them as participants and beneficiaries of trusted health systems that respond to their needs and preferences in humane and holistic ways *(3)*. This approach acknowledges the experiences and perspectives of health-care providers that may enable or prevent the delivery of people-centred care that is of high quality *(64)*.

In HIV care, several studies have shown that people are willing to travel longer distances to consult a health-care provider with a respectful and caring attitude, and negative health-care worker attitudes contribute to loss to care and poor programme outcomes *(65–67)*. For key populations in particular, experiencing stigma and discrimination in health-care settings is a structural barrier to accessing services *(68,69)*. WHO recommends addressing stigma and discrimination in health-care settings as an important component of ensuring access to HIV care *(70)*.

A systematic review was conducted to identify practical ways to enhance people-centred care for people living with HIV *(71)* (Box 7.2). The review identified 15 studies describing intervention strategies including adults, adolescents *(72)* and children and the following key population groups: sex workers, men who have sex with men, transgender people and people who inject drugs.

Box 7.2 Interventions to improve relationships between patients and health-care providers

Interventions that were found to improve relationships between patients and health-care providers could be classified into the following approaches:

- providing friendly and welcoming services:
  - such as through training providers to make general HIV services more welcoming, providing adolescent-friendly services outside school hours and training providers to welcome patients back into care;
- conducting sensitization training for clinical and non-clinical health-care providers to improve care for key populations:
  - both at the primary care and community levels, which includes issues related to stigma and discrimination;
- offering individualized adherence counselling and patient-centred communication:
  - such as shared decision-making and planning for ART initiation and adherence and supporting change in provider attitudes towards those who have disengaged from care;
- facilitating client education in empowerment and communication skills; and
- providing feedback to health-care workers on patient concerns and evaluation of service quality:
  - such as community score cards, patient feedback mechanisms combined with quality improvement exercises.

Overall, studies reported beneficial effects of these approaches across the HIV cascade including improved ART uptake, adherence and suppression of viral loads.

The Guideline Development Group formulated a new good practice considering the indirect evidence showing that a health system–based perspective and providing a variety of people-centred practices will improve relationships between patients and health-care providers. Providing tools to improve people-centred services may reduce stigma, discrimination and violence against people living with HIV, especially among women, transgender people and other vulnerable groups. Health-care providers should be trained appropriately to ensure that, in addition to improving relationships with patients, they are also capable of supporting women and vulnerable groups in responding to gender or intimate partner violence and in accessing sexual health counselling and support.

7.5 Initiating and maintaining treatment

7.5.1 Initiating ART outside the health facility

Recommendation (2021)

ART initiation may be offered outside health facilities *(conditional recommendation, low- to moderate-certainty evidence)*.

This recommendation is additional to routinely offering ART initiation at health facilities.

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

Community-based HIV testing approaches are a key component of any HIV testing strategy *(9)*. In most settings, if a positive HIV diagnosis is made in the community – for example through mobile health services, community centres, services focusing on key populations and patients' homes – the individual is then referred to a health centre to start treatment *(9)*.

WHO recommends rapidly initiating ART, including starting on the same day of a positive diagnosis, partly because of the large losses previously observed between diagnosis and initiation *(18)*.

Losses to care between community HIV testing and ART initiation are substantial: a systematic review of studies in sub-Saharan Africa found that the proportions linked to care could be as low as 14% for home-based testing and 10% for community-based testing; in some settings, less than one quarter were known to have started treatment *(73)*. The reported reasons for not initiating treatment can include feeling healthy, insufficient social support, HIV stigma, high care-seeking costs and incomplete knowledge of treatment benefits *(74)*. This is of particular concern for vulnerable populations such as women, young girls and key populations, who have a heightened risk of stigma, discrimination and violence. WHO has provided recommendations on how national programmes should work to protect these populations *(70,75)*. A study from South Africa and Zambia found that people testing positive in the community often delayed starting ART because of issues related to the quality of care (including long waiting times, lengthy initiation procedures and lost clinic folders) and the stigma associated with accessing care *(76)*. Other studies have cited lack of time *(77)* and concern about long clinic waiting times as the main reported reasons for not linking to care and starting treatment *(78)*.

A systematic review identified three randomized trials and four observational studies providing evidence that offering ART initiation outside the health facility was associated with an increase in the proportion of people starting ART (RR 1.86, 95% CI 1.29–2.68), increased retention in care at 6–12 months following ART initiation (RR 1.44, 95% CI 1.33–1.56) and increased suppression of viral loads (RR 1.31, 95% CI 1.13–1.61) *(79)*; two studies included in this review included key populations *(80,81)*, and one study included adolescents and young adults *(82)*.

Benefits and harm

Early initiation of ART is associated with several health benefits, including reduced mortality and morbidity and reduced onward transmission *(83)*. The offer to start ART before referral to a health facility has the potential to reduce delays in starting treatment for individuals who are unwilling or unable to be referred to the health facility to start treatment. Although the studies that assessed community ART initiation reported no intervention-specific harm, ensuring that baseline assessments and support are provided either as part of the intervention or on referral to the health facility is important.

Feasibility, cost and cost–effectiveness

When ART initiation is included as a component of existing community activities, additional expertise and resources are needed, as reflected by the studies *(78)*. A randomized trial of community-based ART in South Africa and Uganda included an activity-based microcosting study to estimate the annual per-client cost of community-based ART initiation. The study concluded that community-based ART could cost US$ 275–452 per person with suppressed viral loads, slightly more than the US$ 214–422 per person with suppressed viral loads estimated for the facility-based initiation group *(84)*. Another study, from Malawi, assessed optional home initiation of ART following HIV self-testing and found that the average annual cost per participant who initiated ART was US$ 172 versus an annual cost of providing ART in facilities of US$ 858–1165 *(85)*.

Equity and acceptability

Implementing this recommendation could potentially increase access to treatment for individuals who may experience structural barriers such as criminalization, stigma and discrimination when attempting to access health-care services to initiate treatment. A study among female sex workers in the United Republic of Tanzania found that those receiving community ART initiation were more likely to have started treatment and be retained in care and less likely to have interrupted treatment or feel high levels of internalized stigma *(81,86)*. Evidence for adolescents was limited, and the acceptability is uncertain.

Implementation considerations

Confirmatory HIV testing needs to be ensured before ART initiation, consistent with HIV testing guidance that a single reactive test always needs confirmation *(9)* (see Chapter 2). WHO guidelines recommend a readiness assessment when starting ART, including ART literacy, and clinical assessment that includes CD4 cell count enumeration to determine whether a person has advanced HIV disease and requires further diagnostic investigation and provision of prophylaxis *(18)*. WHO further recommends that nurses be able to initiate ART *(3)*, and this should be facilitated by supportive professional regulations and relevant policies at the national level.

Clients starting ART outside a health facility should be linked to a facility and enrolled in a long-term model of care. ART initiation should also be accompanied by appropriate counselling to ensure that individuals understand the importance of lifelong adherence and receive appropriate support. For those who are not ready to start, referral for care should be provided. Initiating ART outside a health facility needs to be accompanied by appropriate measures to ensure that risk assessment and counselling support are provided, including at the time of initiation and in the period thereafter. Additional practical advice may need to be provided on the administration and storage conditions of ARV drug formulations for infants and younger children; community health-care providers should be trained to provide effective counselling to caregivers to support such requirements *(87)*. In addition, ensuring that adolescents are linked to psychosocial care and that children and parents are supported with disclosure and age-appropriate treatment literacy is important.

Implementation of community ART initiation should consider health system requirements for supporting ART delivery at the community levels, including adequate drug supply, laboratory services, training and supervising health personnel, providing preventive therapy and referral mechanisms for those who need higher-level care. Such adaptations may require a phased approach (for example, by starting implementation in settings in which community prevention and testing activities have been established). The provision of community HIV care should be included in national initiatives to ensure the quality of care.

Research gaps

Research is needed to improve understanding of client preferences about where to start ART and how to link to care by age, population and setting *(88,89)*. Tools to support initiation outside the health facility need to be identified and evaluated. Evidence shows substantial variability in the size of the community treatment team, and implementation research would be valuable in defining the optimum staffing complement and minimum set of skills required. Evidence on how ART initiation outside the facility affects household spending and catastrophic costs would also be of value.

7.5.2 Rapid initiation of ART, including same-day start

Recommendations (2017)

Rapid ART initiation[a] should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment *(strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).*

[a] Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start *(strong recommendation: high-certainty evidence for adults and adolescents; low-certainty evidence for children).*

Source: *Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy (18)*

Good practice statement (2021)

The offer of same-day ART initiation should include approaches to improve uptake, treatment adherence and retention such as tailored patient education, counselling and support.

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

In 2017, WHO strongly recommended that rapid ART initiation be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment, with the offer of same-day start for people who are ready *(12)*. This recommendation was supported by evidence showing that rapidly initiating ART leads to an increased likelihood of starting treatment and improved suppression of viral loads and retention in care and may lead to reduced mortality *(90)*. WHO also strongly recommends that nurses be able to initiate and maintain ART *(3)*.

The uptake of this recommendation in national policy is variable. Several countries have not adopted this recommendation in national guidance, and some *(91)* but not all *(92,93)* studies have reported poorer retention in care when ART is started on the same day compared with less rapid ART initiation. Patient perspectives have highlighted the importance of good counselling and non-judgemental, respectful personnel *(94)*.

A systematic review was conducted to identify approaches that support accelerating the offer or uptake of ART after diagnosis among people living with HIV. The review identified 26 studies; 11 were conducted in general populations and three among pregnant women, 10 included key populations (seven included men who have sex with men, two people who inject drugs and one female sex worker) and two included adolescents.

Many strategies were examined, and these could be classified into (1) strategies targeting clients, (2) strategies targeting health-care providers and (3) strategies targeting the health system. Evidence indicated that all these approaches were associated with increased uptake of ART, suppression of viral loads at 12 months and retention in care at 12 months *(95)*.

The systematic review identified a diversity of interventions to improve uptake and outcomes following same-day ART initiation; some of these interventions provided indirect evidence of benefit for other aspects of HIV care. This diversity of direct and indirect evidence provided high certainty in the overall benefit of providing approaches to improve uptake, treatment adherence and retention, and this led the Guideline Development Group to make a good practice statement. It was considered important to highlight strategies targeting clients, health care providers, and the health system. The most commonly assessed interventions are detailed in Table 7.1.

Table 7.1 Evidence-informed approaches to supporting same-day ART initiation at the level of the client, provider and health system

Strategies targeting clients		Strategies targeting health-care providers	Strategies targeting the health system
Pre-ART initiation	Reduce administrative requirements to initiate ART	Provider training on rapid ART initiation	Reduce the number of pre-ART sessions
	Reduce pre-ART psychosocial requirements	Provider training on counselling	First ART counselling on the day of HIV testing
	Aim to improve pre-ART counselling content and delivery	Provider supervision, coaching and mentorship	Increase the duration of pre-ART sessions
	Promote shared decision-making	Provider performance feedback	Expedite the scheduling of appointments to initiate ART
	Increase duration of pre-ART sessions	Provide standard operating procedures and guidance documents	Provide ART first starter pack immediately with no pharmacy waiting time
	Navigation during ART initiation visit	Provide decision support tool (checklist or algorithm)	Point-of-care CD4, TB testing and diagnosis
	Incentives		
Post-ART initiation	Appointment reminders		
	Short-term ongoing navigation and support		
	Intensified post-ART counselling		
	Increased duration post-ART initiation clinical visit		
	Incentive to attend post-ART initiation visits		

7.5.3 Frequency of clinical visits and ART pick-up

Recommendations (2021)

People established on ART should be offered clinical visits every 3–6 months, preferably every six months if feasible[a] *(strong recommendation, moderate-certainty evidence).*

[a] When routine clinical consultations are due, they should be coordinated with planned medicine pick-ups to reduce visit frequency.

People established on ART should be offered refills of ART lasting 3–6 months, preferably six months if feasible[b] *(strong recommendation, moderate- to low-certainty evidence).*

[b] ARV drug supply management should be strengthened to ensure the availability of ARV medicine and prevent stock-outs in the context of less frequent medication pick-ups.

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

In 2016, WHO recommended clinical visits every 3–6 months and dispensing ART lasting 3–6 months for people established on ART *(3)*. Two distinct recommendations were made to underscore the point that clinical visits and medication pick-up should be considered separately. These recommendations have been broadly adopted by national guidelines, with clinical visits and medication pick-up every three months most commonly adopted according to country surveys *(51,96)*.

A systematic review assessed the evidence on outcomes associated with different frequencies of clinical visits and refills of ART *(97)*. The review identified three randomized trials and three observational studies comparing clinic visit frequency at three and six months and found no difference in retention in care (RR = 0.99, 95% CI 0.94–1.03, low-certainty evidence) or suppression of viral loads (RR = 1.02, 95% CI 0.86–1.21, low-certainty evidence). The review also identified three studies, including one randomized trial, comparing ART dispensing frequency and found no difference in retention in care (RR = 1.00, 95% CI 0.98–1.02, moderate-certainty evidence); suppression of viral loads at six months was marginally reduced in one study *(35)* but similar in the other two studies *(55,98)*. One study across six African countries reported that children and adolescents who transitioned to multi-month prescribing maintained favourable outcomes in terms of death, retention, adherence, immunosuppression and suppression of viral loads *(51)*.

Benefits and harm

For people living with HIV who are established on ART, a frequency of clinical visits and dispensing of ART of 3–6 months is associated with improved outcomes compared with monthly schedules. The certainty of the evidence was low to moderate. Some of the evidence supporting these recommendations came from observational studies with methodological limitations, and there was important variability in outcomes across studies.
No harm was identified.

Feasibility, cost and cost–effectiveness

Many countries have adopted the previous WHO recommendation of clinic visits and ART dispensing every 3–6 months, demonstrating feasibility across a diversity of settings *(51,96)*. WHO has also recommended reducing client contact with health services as a way to maintain essential health services during periods of service disruption *(99)*. Differentiated service delivery for HIV treatment, including reduced visit frequency and increased ART refills, saves substantial patient travel costs and greatly reduces the time required to receive ART, including time spent on transport, waiting in the queue or having a clinic visit *(100)*. Reducing the visit frequency also reduces health system costs, making this a cost-saving intervention.

Equity and acceptability

A review of relative patient preferences among adults living with HIV found that, compared with monthly drug refills, people living with HIV preferred longer intervals but showed no strong preference for three-month compared with six-month refill frequency *(67)*. The Guideline Development Group judged that providing the option of less frequent health service interaction has the potential to increase equity by improving opportunities to access care for vulnerable and mobile populations.

Implementation considerations

Reducing the frequency of drug dispensing requires adequate drug supply and the possibility for appropriate storage for clients, including for community ART delivery. Consideration should be given to harmonize and optimize scheduling while ensuring patient choice and linkage to other key services, including viral load and other laboratory investigations and dispensing of medications for TB preventive treatment and chronic conditions. Extended refills should be considered for children older than two years when the dose is adjusted less frequently *(21)*, since younger children need to attend health services for routine services such as immunization. Additional models of community support may need to consider clinic visits for certain groups at greater risk of facing adherence challenges and those at increased risk of other conditions as a result of complications from pregnancy, such as members of key populations, adolescents and pregnant and postpartum women as well as individuals or groups requiring special care to prevent or treat pregnancy-related risks, illness and death.

Research gaps

Evidence is needed on outcomes associated with less frequent clinical visits and/or drug refills (beyond six months) for various populations. In particular, there are contexts in which annual clinical visits are the standard of care and may both benefit clients and reduce costs for health systems.

7.5.4 Adherence support

Recommendation (2016)

Adherence support interventions should be provided to people receiving ART *(strong recommendation, moderate-certainty evidence)*.

The following interventions have demonstrated effectiveness in improving adherence and suppression of viral loads:

- **peer counsellors** *(moderate-certainty evidence)*;
- **mobile phone text messages** *(moderate-certainty evidence)*;
- **reminder devices** *(moderate-certainty evidence)*;
- **cognitive behavioural therapy** *(moderate-certainty evidence)*;
- **behavioural skills training and medication adherence training** *(moderate-certainty evidence)*; **and**
- **fixed-dose combinations and once-daily regimens** *(moderate-certainty evidence)*.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

Background

Adherence to ART is the primary determinant of whether viral loads are suppressed and of the risk of transmission, disease progression and death *(101–103)*.

Suboptimal adherence is a major challenge worldwide and is associated with a diversity of individual, interpersonal, community and structural factors. The most frequently reported individual barriers across all age groups include forgetting, being away from home and a change to daily routine. More than 15% of the people receiving ART report that depression is a barrier to adherence across all age categories, and adults and adolescents commonly report alcohol and substance misuse as a barrier. With respect to contextual barriers, secrecy or stigma is a commonly cited barrier to adherence, reported by more than 10% across all regions. Health service–related barriers are frequently reported, including distance to the clinic and stock-outs *(104)*. Specific population groups that face additional challenges to adherence include pregnant and postpartum women, adolescents, infants and children, key populations and people with mental health and substance use disorders.

Rationale and supporting evidence

A systematic review and network meta-analysis identified 85 randomized trials of interventions to improve adherence *(105)*. The review found moderate-certainty evidence that peer counselling results in improved adherence and suppression of viral loads. Peer-based interventions are generally well accepted, especially among adolescents who find that hearing experiences and learning from others facing the same challenges are critical for supporting adherence and engagement in care. Other interventions found to significantly improve adherence include SMS messages and cognitive behavioural therapy.

Supportive interventions

Several interventions may be of value in addressing specific challenges that affect adherence and/or suppression of viral loads (see the recommendations above).

Nutritional support

Nutritional assessment, care and support are essential components of HIV care. Studies have shown that severe food insecurity predicts disengagement from care, and persistent severe food insecurity is associated with suboptimal adherence to ART and failure to suppress viral loads *(106,107)*. Providing nutritional support to people receiving ART can reduce the risk of non-adherence among food-insecure individuals *(15,108)*. HIV programmes should ensure that existing national policies on nutritional support are observed to maximize adherence to ART and achieve optimal health outcomes, especially in food-insecure settings. Nutritional support could include nutritional counselling, cash transfers, subsidizing food costs and/or food vouchers.

Financial support

Financial support can reduce the risk of non-adherence and improve viral suppression *(109–111)*. Programmes and care providers should consider a broader programmatic approach for reducing the costs of care for people living with HIV that includes avoiding out-of-pocket payments at the point of care (including drugs, diagnostics and clinical services), supporting transport costs, decentralizing care and reducing the frequency of health facility visits. Programmes need to consider the ethical and equity implications of providing financial support and non-monetary incentives for people living with HIV. Standardized criteria for supporting people receiving ART may need to be developed based on national income levels.

Implementation and population considerations

Pregnant and postpartum women

The pregnancy and postpartum period presents significant biological, social and economic challenges that may affect treatment adherence. An estimated one quarter of pregnant women have inadequate ART adherence, and this is higher during the postpartum period *(112)*. Pregnancy-related conditions such as nausea and vomiting may negatively affect treatment adherence. Additional factors also include required care for a positive pregnancy experience, in which antenatal care models recommend a minimum of eight contacts with the health system to reduce perinatal mortality and improve women's experience of care. Pregnant women must be given choice of where to receive ART care, but this should be carefully coordinated with the required antenatal care contacts to avoid missed opportunities to obtain both high-quality and patient-centred antenatal care and ART care. Other individual factors include suboptimal understanding of HIV, ART and interventions to prevent mother-to-child transmission, lack of disclosure to the partner, family and community, disclosure and fear of stigma and discrimination *(113)*. Service delivery barriers include poor-quality clinical practices, gaps in provider knowledge and training, poor access to services and health-care worker attitudes *(114,115)*.

Adolescents

Achieving optimal ART adherence and viral suppression outcomes remain a major challenge among adolescents and youth *(116)*. An estimated 38% of adolescents globally are suboptimally adherent to ART, with substantial regional variation *(117)*. In addition to common challenges to adherence, adolescents face specific challenges such as peer pressure, the perceived need to conform and inconsistent daily routines *(118,119)*. Secrecy and stigma have been reported as important causes of suboptimal adherence among adolescents, with caregiver support, peer support groups and knowledge of HIV status reported as facilitators *(104,120)*. For adolescents who are transitioning from paediatric to adolescent care, additional challenges may include assuming increased responsibility for their own care, issues relating to disclosure to peers or partners, difficulties in navigating the health-care system, lack of links between adult and paediatric services and inadequately skilled health-care providers *(121)*.

Infants and young children

Successfully treating a child requires the commitment and involvement of a responsible caregiver. Parents and other family members of children living with HIV may themselves be living with HIV, and suboptimal HIV care and treatment for family members could result in suboptimal care for the child. Other challenges include lack of nutrition support, limited choice of formulations for children, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements and difficulties in swallowing tablets *(104,122–125)*.

Mental health and substance use

People living with HIV with uncontrolled depressive symptoms are more likely to have poor adherence to ART *(126)*. Depression and anxiety disorder are among the most common mental health disorders associated with suboptimal ART adherence *(127–129)*. Adherence is complicated by mental health comorbidity that results in forgetfulness, poor organization and poor comprehension of treatment plans. Counselling for HIV and depression and appropriate therapies for people with mental health disorders can help to improve adherence.

Use of alcohol and other substances may also contribute to poor adherence to ART. Alcohol and substance use can lead to forgetfulness, poor organization and diversion of monetary resources *(130,131)*. Treating people for depression and managing substance use disorders can improve HIV treatment outcomes *(132)*. WHO recommends treating people with depression and substance use disorders regardless of HIV status. Other key services for people living with HIV who use drugs, such as needle and syringe programmes and drug substitution therapy, provide further opportunities to support adherence.

Key populations

In many settings, key populations face multiple challenges related to stigma and discrimination that can affect access to health services, all of which may negatively affect adherence *(133,134)*. Service delivery approaches to improve engagement in care for key populations, including peer support, are a critical gap.

7.5.5 Monitoring adherence to ART in routine programme and care settings

Good practice statement (2021)

Viral load for treatment monitoring should be complemented with non-judgemental, tailored approaches to assessing adherence.

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

WHO strongly recommends that adherence support interventions be provided to people receiving ART *(3)*. Viral load monitoring is the gold standard for monitoring adherence and confirming treatment response. Other approaches to monitoring adherence should be considered as a way to provide additional information about the risk of failure to suppress viral loads or to support daily tablet-taking behaviour in settings in which viral load testing is not available. Knowledge of adherence can support decisions about whether a recipient of care is eligible for simplified models of service delivery and whether to switch treatment regimens when viral load is unsuppressed.

WHO further recommends that, following an initial high viral load (exceeding 1000 copies/mL), an enhanced adherence intervention should be carried out before conducting a second viral load test. This has been shown to lead to resuppression for about half the people receiving ART, avoiding unnecessary switching of treatment *(135)*.

Simple, affordable measures suggested by WHO to measure adherence include pill counts, pharmacy refill records and self-reporting (Box 7.3) *(136)*. A systematic review identified 50 studies to assess the comparative diagnostic accuracy of these adherence measures *(137)*. Overall, the review found that all adherence measures had low sensitivity for identifying people who are non-adherent and have unsuppressed viral loads. For self-report, asking five or more questions as part of the assessment tended towards providing higher sensitivity in diagnosing viral non-suppression. Composite adherence measures, such as combining self-report with pharmacy refill or tablet count, appeared to provide higher sensitivity.

The Guideline Development Group determined that adherence measures have clear value as an opportunity to discuss issues relating to treatment with people receiving ART and to identify potential barriers to maintaining adequate adherence and areas in which support may be needed.

Box 7.3 Simple, low-cost approaches for measuring adherence

Pharmacy refill records provide information on when people pick up their ARV drugs. Some studies *(138–140)* have found that pharmacy records are a more reliable measure than self-reported adherence.

Self-reported data are easy to collect and can be a useful adjunct to estimating non-adherence but are subject to recall bias *(136)*. Counselling on the importance of remembering ART doses and an environment that promotes and enables honest reporting of non-adherence are critical components. Self-report has been found to be a more reliable predictor of failure to suppress viral loads when the recall period was within one week *(141)*.

Pill counts may help to assess adherence. Pill counts may not be feasible in routine care settings. Pill count has been found to perform better when combined with self-reported adherence *(142)*.

A key value of all these approaches is that they encourage discussions about adherence with people receiving ART.

Specific population groups face additional challenges to adherence, and these should be considered when implementing the recommended interventions. People receiving ART face a range of individual, interpersonal, community and structural barriers to adherence, including issues related to social identity, gender norms, stigma and medical pluralism; unwelcoming health services; and the need for emotional, practical or financial support for long-term engagement and adherence *(104,111)*.

Effective monitoring of adherence requires a combination of approaches based on human and financial resource capacity, acceptability to people living with HIV and health-care workers and understanding of the local context.

Research gaps

Further research is needed to determine:

- optimal ways to proactively monitor adherence and identify through simple triage the people in greatest need of adherence support;
- the most accurate measures of adherence to ART that are feasible in settings with limited resources to complement viral load testing;
- interventions to support adherence in populations at heightened risk of suboptimal adherence (children and adolescents, pregnant women, men who have sex with men and people who inject drugs);
- potential synergistic effects of combining two or more interventions that could affect individual, social support and health system factors; and
- the effectiveness of long-acting ART in improving adherence and suppression of viral loads.

7.6 Continuity of care

7.6.1 Retention in care

Recommendation (2016)

Programmes should provide community support for people living with HIV to improve retention in HIV care *(strong recommendation, low-certainty evidence)*.

The following community-level interventions have demonstrated benefit in improving retention in care:

- **a package of community-based interventions**[a] *(children: low-certainty evidence; adults: very low-certainty evidence)*;
- **adherence clubs**[b] *(moderate-certainty evidence)*; and
- **extra care for high-risk people** *(very-low-certainty evidence)*.

[a] Patient advocates, treatment and peer support interventions providing adherence and psychosocial support in the community.
[b] Peer support, distribution of ARV drugs and assessment by non-clinical or lay health-care providers.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

Background

Disengagement from care undermines programme and patient outcomes. Data from programmes across sub-Saharan Africa shows that, five years after starting ART, almost a fifth (19%) had stopped ART and 15–20% had died *(4,143)*. Retention in ART programmes is a major challenge in all settings and across populations, specifically children and adolescents, postpartum women and men *(144)*. Multiple factors may play a role in disengagement from care, including male sex, unemployment, lower educational status, advanced HIV disease, poor adherence, nondisclosure, distance from a clinic and lack of understanding of the need for lifelong care *(145)*.

Rationale and supporting evidence

A systematic review identified seven studies (one individual randomized controlled trial, one cluster-randomized controlled trial and five cohort studies) that evaluated community-level interventions to strengthen retention in HIV care: a package of community-based interventions, adherence support clubs and providing extra care for high-risk patients *(146)*. A strong recommendation was made despite low-certainty evidence because the balance of benefit greatly outweighed the potential harm, the degree of acceptability to people living with HIV and the programmatic benefits of implementing interventions that result in positive patient and programmatic outcomes.

Package of community-based interventions

Community-based interventions identified as benefitting retention in HIV care included: support centred on the needs of the individual, counselling and psychosocial support by lay adherence counsellors or patient advocates and family and peer support. Lay counsellors or patient advocates assisted with linking health facilities with communities, providing counselling and patient-centred support and visiting people in their home environment. One cohort study included children and adolescents (younger than 16 years) and demonstrated significantly increased retention at 36 months *(147)*.

Adherence clubs

A systematic review identified one cohort study evaluating how facility-based adherence clubs affected loss to follow-up or death at 40 months, with a significant reduction compared with standard care *(148)*. More recent studies have reported outcomes of adherence clubs that are equivalent to or better than standard care, including for adolescents and postpartum women *(25,55,149,150)*.

Extra care for people with advanced HIV disease

The systematic review identified one cohort study from Kenya that evaluated how nurses and non-clinical health-care workers providing weekly or biweekly contact with people with advanced HIV disease (defined in the study as CD4 count <100 cells/mm^3) affected mortality *(151)*. These patients met a non-clinical health-care worker for brief assessment and were referred to a nurse where necessary, in addition to peer support and distribution of ART every two months and a yearly follow-up review with a clinician. Long-term follow-up and death were significantly reduced at 40 months. A trial from the United Republic of Tanzania and Zambia found that people with advanced HIV disease who were given early adherence support together with diagnostics for TB and cryptococcal meningitis had better retention and survival than those receiving standard care *(152)*.

Cost and cost–effectiveness

The cost of implementing community-level interventions varies by setting and depends on whether community-based health programmes are already established. Generally, costs related to training and remunerating lay health-care providers are much less than the cost of care provided at the facility level and care provided by health-care workers. Costs related to community support, peer support and support by patient advocates are often related to training and orienting these cadres and support groups.

Equity and acceptability

A qualitative evidence synthesis highlighted key interventions that were acceptable in improving retention *(153)*. These included lay health-care workers providing support (moderate certainty), especially if they were also living with HIV; family and friend support (moderate certainty); mobile health interventions (moderate certainty) and developing positive and non-judgemental relationships with those implementing the intervention (moderate certainty).

Population considerations

Pregnant and breastfeeding women

For pregnant women living with HIV, the transition from antenatal care and maternal, newborn and child health services to ART care is a potential point for loss to follow-up. A systematic review identified 10 studies (one cluster-randomized controlled trial, three individual randomized controlled trials and six cohort studies) that evaluated interventions to improve postpartum retention of women living with HIV *(154)*. Most of the studies reported outcomes in the immediate postpartum period. Moderate-certainty evidence supported using phone calls and SMS messaging to improve retention in the early postpartum period (6–10 weeks), but long term outcomes were not reported. Evidence on the cost–effectiveness of interventions to improve retention in care of postpartum women is also very limited. Several reviews report positive effects of various mHealth approaches and associated technologies are low cost *(155–158)*.

The period of transition from maternal, newborn and child health services to HIV care clinics is often a critical point in which many women and their infants discontinue care. Several countries are implementing interventions with evidence of benefit, including assigning district-level focal points, active patient tracing and financial support for transport. Many programmes are implementing community-based interventions: peer support such as mothers-to-mothers programmes and peer adolescent support groups for adolescent pregnant women living with HIV. Structured counselling sessions and telephone reminders may also potentially support the process of transition.

An increasing number of women living with HIV who become pregnant are clinically stable on ART and access their care through a differentiated ART delivery model. While they are pregnant and during the early postpartum period, these women require additional health-care visits. They should have the choice to continue receiving their ART through the differentiated ART delivery model or to have their ART delivery integrated within their maternal, newborn and child health care. Notably, additional criteria are specific to pregnant and breastfeeding women who choose to access ART in models outside their maternal, newborn and child health care (Box 7.4) *(21)*.

Box 7.4 Additional eligibility criteria specific to pregnant and breastfeeding women for accessing differentiated ART delivery models outside clinic care

- **Women clinically established on ART when conceiving:** already accessing the differentiated ART delivery model plus at least one viral load test of <1000 copies/mL in the past three months and accessing antenatal care.
- **Women initiating ART during pregnancy:** since a woman initiating treatment during pregnancy will only become eligible to enter a differentiated ART delivery model in the postpartum period, an HIV-negative result for her infant with a NAT at six weeks and evidence of accessing infant follow-up care are additional requirements.

Children

Successful treatment of children, especially younger children, requires that caregivers understand the importance of adherence and retention in care. Several factors affect adherence and retention in care, including appropriate ARV drug formulations, centralized paediatric care, adequate psychosocial support and effectively disclosing HIV status to children.

WHO recommends age-appropriate disclosure to children *(159)*. Other solutions include: supporting caregivers to attend for regular follow-up by providing adherence counselling and appointment reminders; psychosocial support to address issues of stigma and fear; assisted disclosure – caregiver buddy support on the disclosure process and reinforcing to caregivers the importance of disclosing to the child, which can begin early with age-appropriate messaging and tools.

Adolescents

Frequent clinic visits, fear of stigma, time spent waiting for services and having to miss school discourages adolescents' engagement in care and may lead to poor adherence and disengagement from care *(120,160)*. Negative attitudes of health-care workers, concerns about privacy and confidentiality and limited opportunity to discuss their concerns also act as barriers to retention for young people. Distance to facilities and out-of-pocket expenses may restrict engagement. Service delivery models beyond the facility that support adolescents in engaging in care, such as peer-based interventions and community-based services, should be considered. Young people value peer interventions highly. Adolescent-friendly health services should be implemented to improve quality (see section 7.11).

Consider:

- providing adolescent services at specific times or in separate areas with flexible appointment systems that accommodate school hours;
- providing comprehensive services that address multiple needs, including psychosocial support and sexual and reproductive health; and
- closely monitoring adolescents' engagement in care, rapidly and proactively following up and implementing strategies for re-engagement.

Men

A systematic review of 31 studies found that men had a 46% increased hazard of death while receiving ART compared with women *(11)*. This is partly explained by the fact that men tend to be diagnosed later and are more likely to start ART late. Men in settings with a high burden of HIV infection and men from key populations are consistently less likely to know their HIV status than women. In 2021, WHO issued a policy brief highlighting the need to improve coverage of HIV testing among men. This policy brief emphasizes that, in settings with a high burden of HIV infection, efforts are needed to test more men in both general and key populations. In settings with a low burden of HIV infection, HIV testing services should give priority to men from key populations; men with sexually transmitted infections; men with confirmed or suspected TB; men whose partners have HIV; and men who have HIV-related symptoms or indicator conditions *(161)*.

In several settings, initiatives to improve men's engagement in care have focused on engaging them in services for preventing mother-to-child transmission. Innovative service delivery models are essential to improve men's access to HIV care services and ART initiation. Programmes need to routinely disaggregate data by sex to better monitor access to and outcomes of treatment for both men and women.

Key populations

Specific consideration, especially in settings in which people are criminalized because of their behaviour or identity, requires delivery community and peer-based options to support people to retain care.

People in prison and other closed settings

Implementing safety measures to assure the continuity of care is critical, such as providing two months of ART to people who move back into the community to address issues such as housing, health insurance and health-care provider.

Implementation considerations

No single model of community or peer support works in all settings, and programmes need to adapt such interventions to the local context. Some clients may choose not to receive services in the community because of concern about stigma and discrimination. Community interventions require linkage with health facilities for smooth transfer and referral, when necessary, and strategic planning and resourcing for sustainability. Community-level programmes still need to be integrated into national health sector plans in many settings.

Research gaps

Implementation research and evaluation of the different models of community-level support in different contexts are necessary to further guide programmes. Effective strategies are needed to support transitioning across care-delivery points for men, postpartum women, adolescents and children. Further data on the cost of implementing community-level interventions in different settings will guide national policy.

7.6.2 Tracing and re-engagement in care

Recommendation (2021)

HIV programmes should implement interventions to trace people who have disengaged from care and provide support for re-engagement *(strong recommendation, low-certainty evidence)*.

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

WHO guidelines strongly recommend that programmes provide community support for people living with HIV to improve retention in HIV care *(3)*. Poor retention undermines positive programme outcomes, including reducing mortality and achieving sustained population suppression of viral loads. Although many programmes have adopted these recommendations to support retention, loss to follow-up remains substantial in all regions, and especially in southern Africa, affecting all age groups *(4,143,144)*. Although some individuals who are no longer engaged in care for various reasons have died, recent data suggest that many individuals who are successfully traced are alive *(161)*, and many are willing to re-engage in care. WHO recommends patient tracing as one of many potential interventions that could improve linkage between diagnosis and ART initiation *(3)*.

A systematic review assessed activities to trace individuals who have disengaged in care and to identify interventions to support re-engagement in care; the review identified 37 studies, eight of which included children and adolescents *(163)*. Overall, among those who were alive, 58% (95% CI 51–65%) re-engaged in care. Tracing and re-engagement action appeared to be more successful when people were traced soon after a missed visit compared with a longer period of disengagement. Approaches to tracing included remote communication (phone, text messages, mail and email), in-person tracing and a combination of both approaches.

Benefits and harm

Tracing activities can successfully re-engage people in care and achieve resuppression of viral loads. The certainty of the evidence was judged to be low, mainly because of important heterogeneity in outcomes across studies leading to imprecise estimates of benefit.
The literature did not identify any important harm. Although tracing activities carry the hypothetical risk of inadvertently disclosing HIV status that could lead to intimate partner violence, discrimination and stigma, this risk is considered small and is outweighed by the benefits of re-engaging individuals into care and onto life-saving ART, without which there would be increased illness and death. The Guideline Development Group made a strong recommendation despite low-certainty evidence given the confidence in the health benefit for people returning to care and minimal harm associated with tracing and re-engagement activities.

Feasibility, cost and cost–effectiveness

Most reports described the tracing activities undertaken by existing health facility personnel; in some cases, social workers and community health workers formed part of the tracing team, and personnel were trained. Other associated costs include establishing systems to trace and support re-engagement. In-person tracing requires resources to support the travel of tracing teams and human resources with appropriate training and remuneration, including the potential need to undertake multiple tracing attempts.

Equity and acceptability

Tracing in the absence of consent may be considered intrusive and may not be accepted by people who have disengaged from care (with various motivations). Tracing must also be sensitive to the need to respect human rights and confidentiality and avoid inadvertently disclosing HIV status. The Guideline Development Group judged that the intervention would probably increase equity and is probably acceptable to most people living with HIV if delivered in a non-judgemental approach. Clients should be provided with the opportunity to consent to tracing when ART follow-up is discussed during counselling and at ART initiation.

Implementation considerations

Support for re-engagement in care can include interventions directed towards people living with HIV, such as peer or health-care provider outreach and navigation back to care as well as towards health-care providers and health facilities (through systems to alert health-care providers that people have disengaged). Interventions could include reminders (such as phone calls or text messages), economic interventions (such as financial incentives or conditional cash transfers), case management or policy interventions, with steps taken to ensure confidentiality. Programme- or facility-level confidential contact details should be kept up to date to ensure successful tracing if and when required. When considering tracing people who are not engaged in care, adequate assessment of the risks to vulnerable and key populations is critical. For example, women are subject to increased levels of both intimate partner and gender-based violence in the context of HIV, and appropriately training health-

care providers is therefore essential *(164)*. It is critical to understand both general and local reasons for failures of retention; these are far more predictive than sociodemographic factors such as age and sex *(165)*.

The criteria for tracing and recall should consider those who are seven or more calendar days late for a scheduled appointment. Although efforts should be made to trace everyone who has missed appointments and/or has abnormal results, the following groups should be given priority: (1) people initiating treatment in the past six months with advanced HIV disease, (2) people with abnormal results, (3) people not initiating treatment and (4) people overdue for clinical consultations or laboratory tests.

A non-judgemental approach is essential to supporting people in returning to care; this requires reducing system barriers and improving interpersonal communication by developing the capacity of health-care providers. The Welcome Back service established by Médecins Sans Frontières and the Department of Health of South Africa provides a strong example of such an approach combining medical and psychosocial support for people who have disengaged from care *(162,166)*.

Research gaps

Several studies have described the most common reasons for disengaging from care either before or after initiating ART *(74,165,167,168)*. Research is needed to tailor support that responds to these drivers to minimize disengagement and support re-engagement at different stages along the continuum of care. Qualitative research is important to understand the most acceptable and effective methods of tracing and re-engagement. In addition, this research should include disaggregated approaches based on the population group (such as key populations), gender and age.

7.7 Task sharing

7.7.1 Task sharing for initiating and maintaining ART

Recommendation (2016)

The following recommendations apply to all adults, adolescents and children living with HIV.

- **Trained non-physician clinicians, midwives and nurses can initiate first-line ART** *(strong recommendation, moderate-certainty evidence).*
- **Trained non-physician clinicians, midwives and nurses can maintain ART** *(strong recommendation, moderate-certainty evidence).*
- **Trained and supervised community health workers can dispense ART between regular clinical visits** *(strong recommendation, moderate-certainty evidence).*
- **Trained and supervised lay health-care providers can distribute ART** *(strong recommendation, low-certainty evidence).*

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

Background

The number of available health-care providers remains inadequate in many settings with a high burden of HIV. Task sharing involves redistributing tasks within health workforce teams. Specific tasks are reassigned to health-care workers with shorter training and fewer qualifications to optimize the available human resources. Although increasing the number of health-care personnel is also crucial, clinical tasks need to be shared to ensure that enough health-care workers are available.

Since 2013, WHO has made a series of recommendations on task sharing relating to initiating and maintaining ART for adults, adolescents and children. These recommendations are supported by randomized trials and observational studies *(169–171)*. Overall, the evidence shows comparable clinical outcomes and reduced rates of loss to follow-up when nurses or non-physician clinicians initiate or maintain people on ART or when community health workers maintain people on ART, relative to physicians performing these tasks. Quality of care is ensured by providing training, mentoring and supervision for nurses, non-physician clinicians and community health workers, clear referral pathways and effective monitoring and evaluation systems.

In 2016, WHO further recommended that trained community health workers be able to dispense and distribute ART. A meta-analysis of findings from two cluster-randomized trials comparing dispensing ARV drugs between pharmacists and non-pharmacists found comparable clinical outcomes and improved retention comparing people who received care from a community-based team and those who received care from health-care professionals at a health facility *(59,170,172)*. The evidence was rated as low certainty because of indirectness, since the lay health-care providers were part of a wider community-based intervention with additional elements that supported the success of the intervention. Nevertheless, the Guideline Development Group strongly recommended that trained and supervised lay health-care providers be able to distribute ART to adults, adolescents and children living with HIV, citing existing programme experience of trained and supervised community health workers and lay health-care workers providing HIV testing, care and treatment services. In addition, the Guideline Development Group cited important examples within the broader health sector in which community health workers, with minimal training, are entrusted to provide curative and preventive care in maternal, newborn and child health services, malaria diagnosis and treatment and TB care.

Benefits and harm

The public health benefits of lay health-care providers distributing ARV drugs are increasing the overall number of providers to overcome shortages of facility personnel, reducing facility congestion and providing services closer to communities that support retention in care. If ARV drug supply and stock management are not reliable, lay personnel distributing ARV drugs outside health facilities may increase distribution sites and potentially aggravate stock-out. Neither of the two studies included people with comorbidities or children. The Guideline Development Group advised that the dose for growing children can be safely adjusted during clinic visits with maintenance treatment at the community level.

Cost and cost–effectiveness

Costs for training and other costs associated with introducing community ART distribution may be initially increased. However, studies report substantial user costs when they are required to travel to centralized health services to collect medication. A study from Uganda reported that the cost to beneficiaries receiving hospital-based care was three times higher than for people who received home-based care *(172)*.

Equity and acceptability

A qualitative evidence synthesis found that task sharing can enhance linkage to care and treatment adherence and helped HIV programmes cope with shortages of professional health-care workers *(15)*. Strengthened relationships between people living with HIV and local communities can empower individuals. In Malawi, people from the community were hired as pharmacy attendants to pre-package and distribute ARV drugs to enhance the capacity of pharmaceutical services, an approach that has facilitated visit spacing and reduced waiting times and health-care providers workload at health facilities *(173)*. All providers should be sensitized to the specific needs of the various people living with HIV groups, including key populations.

Implementation considerations

Initial and ongoing training and mentoring, supportive supervision and administrative planning have been critical to the success of programmes that have implemented task sharing. Programmes adopting these recommendations need to train and establish a system for routine supportive supervision of health-care workers, including lay health-care providers. Adopting task-sharing strategies often requires revising regulatory frameworks and national policies so that new cadres of health-care workers can perform new tasks. WHO recommends that all health-care workers, including community health workers, should be appropriately trained, remunerated and supervised *(174)*, and programme experience indicates that sustaining health services based on volunteerism alone is difficult. National regulatory bodies, professional associations and other stakeholders need to be involved in addressing the scope of practice, roles and responsibilities of health-care workers. Relevant curricula for training the various community cadres must be in place.

The local supply chain system must consider task-sharing responsibilities and community models of ARV drug delivery to ensure adequate stock. The supply management logistic information system needs to incorporate all ARV drug distribution outlets, including community and lay health-care providers' distribution sites (see section 6.13).

7.7.2 Task sharing of specimen collection and point-of-care testing

Recommendation (2021)

Task sharing of specimen collection and point-of-care testing with non-laboratory personnel should be implemented when professional staffing capacity is limited *(strong recommendation, moderate-certainty evidence).*

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

The 2016 WHO consolidated HIV treatment guidelines *(3)* stated that good practice includes trained and supervised non-laboratory personnel, including lay people, being able to collect blood samples through finger-pricks. This statement was made at a time when data comparing the performance of specimen collection and/or testing by non-laboratory personnel versus laboratory professionals were limited. Most data before the 2016 consolidated HIV treatment guidelines focused on point-of-care diagnostic accuracy studies conducted in the laboratory by laboratory professionals.

Since 2016, several additional studies have been published, including the diagnostic accuracy of decentralized and task-shared specimen collection and/or testing with non-laboratory professionals *(175)*. In addition, clinical studies examining how point-of-care testing by non-laboratory personnel affects the people being tested have been published *(176)*. Together, this updated evidence has supported consideration of using point-of-care infant diagnosis and viral load testing to improve health outcomes.

In several settings, trained and supervised lay health-care providers are already conducting HIV testing and collecting blood samples through finger-pricks. In 2015, WHO strongly recommended that lay health-care providers who are trained and supervised be able to independently conduct safe and effective HIV testing using rapid diagnostic tests *(177)*.

Access to diagnostic testing and sample collection remains low in many resource-limited settings, partly because of shortages of human resources, especially in rural settings. The lack of skilled laboratory professionals at health-care facilities and the need to scale up capacity may require sharing the tasks of point-of-care diagnostic testing and sample collection with lower cadres of health-care workers. Task sharing may also increase access to testing for key populations, who may have difficulty in accessing traditional health-care services regardless of professional staffing capacity.

A systematic review identified 65 studies, mainly diagnostic accuracy studies *(175)*. Three randomized controlled trials assessed the clinical impact of point-of-care testing. Most studies (86%) were carried out in Africa. The certainty of the evidence was rated as moderate. Ten types of non-laboratory health-care workers performed nine types of point-of-care tests using 13 assays. Most studies included nurses. The primary outcome observed across most studies focused on the diagnostic accuracy of point-of-care testing performed by non-laboratory personnel *(175)*.

Diagnostic accuracy of point-of-care CD4 count

Compared with laboratory-based testing performed by laboratory professionals, point-of-care CD4 count testing performed by non-laboratory health-care personnel had a mean bias of –35.72 cells/mm^3 (95% CI –57.10 to –14.33) *(175)*. Four studies compared the performance of point-of-care CD4 testing between laboratory professionals and non-laboratory personnel. The performance of each study was within the ±50 cells/mm^3 range, and the overall mean bias was –13.35 cells/mm^3 (95% CI –19.97 to –6.72). One study reviewed the performance of a device-free lateral flow CD4 assay when performed by nurses compared with laboratory-based CD4 testing performed by laboratory personnel *(178)* and found better performance of the test on venous blood (sensitivity = 81.7%; 95% CI 72.3–91.1%; specificity = 82.6%, 95% CI 77.1–88.1%) than on finger-prick specimens (sensitivity = 60.7%; 95% CI 45.0–76.3%; specificity = 89.5%, 95% CI 83.2–95.8%). No statistically significant difference in performance was detected by cadre of health-care worker ($P = 0.11$) or between point-of-care versus laboratory-based testing ($P = 0.11$).

Diagnostic accuracy and clinical impact of point-of-care infant diagnosis

A systematic review provided summary estimates of the diagnostic accuracy of technologies capable of being used at the point of care *(179)*. The performance overall was >98% sensitivity and >99% specificity. Seven of the 11 studies conducted the point-of-care test outside the laboratory. One study compared internal quality control rates and the return of results to caregivers for samples run on a point-of-care infant testing technology between nurses and laboratory-trained personnel to assess how task sharing affects the quality of testing. Failure rates did not differ significantly between non-laboratory testers (137 of 14 830 tests) and specialized laboratory-trained testers (28 of 364 tests) ($P = 0.35$) *(180)*.

Point-of-care same-day testing significantly reduced the time to deliver test results to caregivers *(176)*. In all seven studies *(176)*, the median time between sample collection and the results received by the infants' caregivers was 0 days (95% CI 0–0 days) for point of care, regardless of the test used, the age of the infant or the type of health-care facility. Same-day results were returned 97% of the time for point-of-care testing versus 0% for standard care. For laboratory-based testing, the median time between sample collection and results received by the caregiver ranged from 8 to 125 days, with a median of 35 days (95% CI 35–37 days). Five of seven studies had a median time to the caregiver receiving results exceeding 30 days.

The overall proportion of infants living with HIV initiating treatment within 60 days was 90% using point-of-care testing versus 54% using laboratory-based testing. The odds ratio of initiating treatment within 60 days was 7.9 (95% CI 5.4–11.5).

Three studies reviewed the performance of cryptococcal antigen lateral flow assays when used by non-laboratory personnel *(181–183)*. The non-laboratory personnel correctly identified cryptococcal antigen with 100% sensitivity and specificity in two of the studies. In the third study, when tested on serum samples, cryptococcal antigen lateral flow assays had sensitivity of 93% (95% CI 66–100%) and specificity of 100% (95% CI 88–100%). Two independent readers strongly agreed on the interpretation of results ($P < 0.001$). When trained nurses performed cryptococcal antigen lateral flow assays at the point of care, testing was feasible, had the highest accuracy on serum specimens and may accelerate the prophylaxis and treatment of HIV-associated cryptococcal infections.

In addition, syphilis testing by non-laboratory personnel using the dual HIV and syphilis rapid diagnostic test had agreement of 0.67 (95% CI 0.36–0.97) and specificity of 99.9% (95% CI 99.8–100%) versus laboratory technicians *(184)*. Nursing personnel successfully tested external quality assurance panels using syphilis rapid tests, with sensitivity and specificity exceeding 90%.

Three studies compared the performance of alanine aminotransferase and haemoglobin enumeration tests operated by non-laboratory personnel with laboratory-based technologies operated by laboratory professionals *(185–187)*. Non-laboratory personnel operated both tests comparably to the laboratory-based technologies operated by laboratory professionals. A semiquantitative, visual point-of-care alanine aminotransferase assay performed by nurses had sensitivity of 87% and specificity of 77% compared with a laboratory-based technology operated by laboratory professionals. One study reviewed the performance of creatinine and lactate testing by non-laboratory personnel at two separate clinics. Creatinine testing had mean bias values of –4.5 µmol/L (95% CI –2.09 to –6.42 µmol/L) and –5.5 µmol/L (95% CI –4.49 to –6.42 µmol/L), and lactate testing had mean bias values of 0.01 mmol/L (95% CI –0.10 to 0.13 mmol/L) and 1.1 mmol/L (95% CI 1.04–1.18 mmol/L).

Clinical impact of point-of-care viral load testing

Using point-of-care tests, same-day viral load results were available to clinicians 99% of the time (median time to results being returned: 0 days) and to patients 99% of the time (median: 0 days) *(188,189)*. Using standard care laboratory-based testing, same-day results were available for clinicians <25% of the time (median: 2 days) and for patients <1% of the time (median: 28 days). The observational studies also demonstrated substantially shorter time to return of results to both clinicians and patients using point-of-care testing versus laboratory-based testing. The hazard ratio comparing point-of-care with laboratory-based testing was 11.7 (95% CI 8.9–15.3) for returning the results to clinicians and 17.7 (95% CI 13.0–24.1) for returning the results to patients.

In the randomized controlled trial, 100% of the people identified with non-suppressed viral loads initiated second-line ART following point-of-care testing (median: 0 days) versus 44% (median: 76 days) following laboratory-based testing (risk difference = 56 percentage points, 95% CI 23–88 percentage points; hazard ratio = 11, 95% CI 2–58). The estimated time to any clinical action (either enhanced adherence counselling or initiating second-line ART) was also shorter following point-of-care testing versus laboratory-based testing in observational studies.

Benefits and harm

The Guideline Development Group formulated a strong recommendation based on judgement of the overwhelming benefits of the intervention, including, but not limited to, the following.

- Most settings with limited resources and a high burden of HIV infection lack laboratory professionals.
- Decentralized and task-shared specimen collection expands access to testing (dried blood spot specimens for infant diagnosis and viral load).
- Point-of-care testing leads to more rapid testing, return of results to clinicians and patients and clinical action.
- Fewer health facility visits are needed for caregivers to receive results, and the timing of results is more reliable.

There was no major harm, but more extensive network support and maintenance were needed.

Feasibility, cost and cost–effectiveness

Overall, task sharing of specimen collection and point-of-care testing with non-laboratory personnel was feasible and acceptable. Task sharing would save costs with deployment of personnel with less training for diagnostic testing and sample collection. The most important cost will be training, ongoing supervision and remunerating non-laboratory personnel, albeit at a potentially lower cost compared with laboratory professionals. Decentralization will likely result in increased proportions of non-laboratory personnel required to perform the specimen collection and testing, requiring careful assessment and expansion of human resource capacity.

Equity and acceptability

Task sharing of specimen collection and point-of-care testing with non-laboratory personnel is likely to improve equity, since relying on specialized personnel favours populations in urban settings and increases the transport burden on rural populations, which generally have the lowest incomes. Task sharing may also increase access to testing for members of key populations, who may have difficulty in accessing traditional health services and facility-based services. Further, decentralizing specimen collection and testing, including at community-based sites, may increase access to diagnostics, especially including interventions and technologies capable of returning the results on the same day or more rapidly than laboratory-based testing.

In a systematic review, 58% of non-laboratory personnel indicated that preparing dried blood spot specimens for viral load was very easy, 43% indicated that collecting specimens was easy and 85% indicated that preparing dried blood spots was suitable for non-laboratory personnel *(175)*. Nurses had a 98% success rate of finger-prick blood specimen collection in South Africa. One study reported an ease-of-use score for task sharing point-of-care CD4 testing between 1.7 and 3 on a scale of 1 to 5 (5 being very difficult), and health-care worker trust in the test was measured at 82–100%. Another study found an odds ratio

of 1.9 (95% CI 1.1–3.3) for more rational use of higher-level clinical personnel time when point-of-care CD4 testing operated by lower-level personnel was introduced instead. Further, 95% (95% CI 93–96%) of lay health-care workers rated the point-of-care CD4 technology favourably. All non-laboratory personnel found the point-of-care viral load testing to be easy or very easy to use, and 85% of the respondents indicated that point-of-care viral load testing was suitable or very suitable for non-laboratory personnel. Ninety per cent of non-laboratory personnel said that a syphilis rapid diagnostic test was easy to use, and antenatal care personnel scored the dual HIV and syphilis rapid diagnostic test 2.41 (with 3 being easiest) for ease of use and 2.27 (of 3) for ease of interpretation.

A study in Cameroon, Côte d'Ivoire, Eswatini, Kenya, Lesotho, Mozambique, Rwanda and Zimbabwe conducted structured interviews with health-care workers providing infant testing services and semistructured interviews with national and regional laboratory managers or early infant diagnosis programme managers before and after point-of-care infant testing was implemented *(188)*. Health-care workers found point-of-care infant testing easy to use (74% said it was very simple to run the test), and 93% were very satisfied with the rapid turnaround time and ability to initiate treatment for infants living with HIV sooner.

Implementation considerations

Access to high-quality diagnostic testing should be continually expanded across HIV and other molecular testing needs, ideally combining laboratory-based and point-of-care technologies in an integrated laboratory network. Implementing a wide network of decentralized specimen collection and/or point-of-care testing requires centralized support from national laboratories and programmes to ensure adequate training, mentorship, service and maintenance, continuous quality assurance and accurate data entry at the point of care. In addition, decentralizing specimen collection and task sharing requires expanding human resource capacity. Legal and regulatory issues and policies may need to be adjusted in some countries to support the decentralization and task sharing of specimen collection and testing with non-laboratory personnel. Concurrently, scaling up and building human resource capacity, including strengthening laboratory personnel and capacity, will be critical to expanding diagnostic access. WHO has developed tools and guidelines for human resources for health and recommends an approach to systematically address the dynamics of the health workforce that includes assessing workload indicators among health-care providers.

Research gaps

Additional diagnostic accuracy studies directly comparing the performance of newer point-of-care technologies (infant diagnosis and viral load testing) between non-laboratory personnel and laboratory professionals would be valuable.

7.8 Decentralization

Recommendation (2013)

Decentralization of ART care should be considered as a way to increase access and improve retention in care. The following approaches have demonstrated effectiveness in improving access and retention:

- **initiating ART in hospitals, with maintenance of ART in peripheral health facilities** *(strong recommendation, low-certainty evidence)*;
- **initiating and maintaining ART in peripheral health facilities** *(strong recommendation, low-certainty evidence)*; and
- **initiating ART at peripheral health facilities, with maintenance at the community level** *(strong recommendation, moderate-certainty evidence)*.[a]

[a] The community level includes external outreach sites, health posts, home-based services or community-based organizations. The frequency of clinic visits depends on health status.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: summary of key features and recommendations, June 2013 (190)*

Background

The rapid scale-up of ART programmes has posed significant challenges to health systems in settings with a high burden of HIV infection and limited resources. Many clinics have long waiting times because of the volume of people needing care. Decentralizing HIV care and treatment has been shown to reduce waiting times and bring HIV services closer to people's homes. It can also strengthen community engagement by linking community-based interventions with health facilities and optimize access to services, care-seeking behaviour and retention in care *(191–194)*.

Rationale and supporting evidence

A systematic review identified 16 studies providing evidence that decentralizing ART care, either from hospitals to health centres or from health centres to community-based care, reduces attrition without compromising clinical outcomes. All but one of the studies were carried out in sub-Saharan Africa, and the benefits of decentralization may differ by setting *(192)*.

Implementation considerations

The optimal model for ART decentralization (partial or full) depends on the local context, including the burden of HIV infection and the health-care delivery systems. Programmes should determine which clinical and laboratory services will be available at what level of the health-care delivery system.

Programme managers should consider the attitudes and preferences of those receiving care, the number of people likely to attend decentralized settings and whether decentralization brings services closer to people who would otherwise travel long distances to receive ART.

Decentralization should be accompanied by efforts to strengthen linkage and referral systems. Community-based treatment programmes should be linked with care at health facilities and with adequate laboratory, diagnostics, monitoring and evaluation and drug and supply management systems.

Standards of care should be defined for each level of the health system, including the private sector. The role of each level should match its capacity, and the lines of authority and accountability should be clear and well understood. In many settings, decentralizing ART requires task sharing to ensure an appropriate mix of health-care workers at peripheral facilities. An appropriate regulatory framework (laws, regulations, policies and guidelines) is needed to enable tasks to be performed by different cadres of health-care workers.

Adaptations may be needed for specific populations. HIV care and treatment services for pregnant and postpartum women and HIV-exposed and infected children can be provided in decentralized settings. This is a preferred option if the burden of HIV infection is high and many women and children access health services in primary care settings. In settings with a low burden of HIV infection, a centralized service delivery model with community linkage may be more appropriate. Some groups, such as adolescents and key populations, may choose to receive HIV services in a facility that is not close to their homes because of stigma and disclosure-related concerns. In such settings, health-care providers should incorporate the values and preferences of adolescents and key populations in designing appropriate service delivery models.

7.9 Integrating services

Chronic care requires integrating and linking related services to ensure that comprehensive and consistent care is provided over time, including providing related services in the same settings, systems to share information and effective referrals across settings and providers. Integrating and linking services are likely to reduce missed opportunities for initiating ART, enhance adherence support and optimize retention in care.

7.9.1 Delivering ART in maternal and child health-care settings

Recommendation (2013)

In generalized epidemic settings, ART should be initiated and maintained in pregnant and postpartum women and in infants at maternal and child health-care settings, with linkage and referral to ongoing HIV care and ART, if appropriate *(strong recommendation, very-low-certainty evidence)*.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: summary of key features and recommendations, June 2013 (190)*

Background

Since 2016, WHO has recommended initiating ART to everyone living with HIV regardless of CD4 cell count, including pregnant and breastfeeding women. However, access to ART for pregnant and breastfeeding women living with HIV remains a challenge, as does providing essential HIV services to HIV-exposed uninfected and infected infants and ensuring that services for preventing mother-to-child transmission reach pregnant adolescent girls and young women, female sex workers and women who inject drugs.

Because many women living with HIV only access health services at the time of pregnancy, maternal and child health settings provide a key opportunity to provide access to ART *(195,196)*. In most generalized HIV epidemic settings, maternal and child health services are provided at the primary care level, where pregnant women and children predominantly access health services. WHO recommends offering HIV testing services to pregnant women through provider-initiated approaches as an essential component of maternal, newborn and child health services. WHO also recommends couple and partner HIV testing for all pregnant women and their partners in maternal and child health-care services in generalized HIV epidemics and that such testing be considered for key populations in concentrated and low-level epidemics *(9)*. In addition, in settings with a high burden of HIV infection, retesting is advised for all pregnant women with an unknown or HIV-negative status during late pregnancy (third trimester). Catch-up testing is needed if the first test or retest is missed or delayed. Countries with a high burden of HIV infection could consider an additional retest in the postpartum period for specific districts or regions with high HIV burden or incidence, women from key populations and women who have a partner living with HIV who does not have suppressed viral loads *(9)*.

ART should be available in maternal and child health clinics or easily accessible in a linked model of service delivery. Countries with generalized epidemics may consider a phased approach to providing ART in maternal and child health settings, which may effectively transform such settings into ART sites, giving priority to facilities with the largest burden of HIV and building health systems to ensure uninterrupted ART, good adherence and retention to maintain viral suppression. All pregnant women, regardless of when they start ART, may require more intense monitoring of viral suppression, including conducting viral load testing at 34–36 weeks of gestation (or at the latest at delivery) to identify women who may be at risk of treatment failure and/or may deliver infants at higher risk of perinatal transmission. In addition, a viral load test is recommended for all breastfeeding women three months after delivery and every six months thereafter to detect viraemic episodes during the postnatal period *(197)*.

Not all maternal and child health settings will have capacity to provide long-term HIV care and treatment for women, their partners and infants. These settings will need to assess and decide on the best time for transitioning and linking mothers and their infants to chronic HIV care and from chronic care into maternal and child health settings when the pregnant woman was already receiving ART at the time of conception. Providing choice for where a woman living with HIV receives ART care remains important and should not interfere with efficient provision of quality and person-centred antenatal care. Issues to consider in the assessment may include the capacity and quality of HIV care in the maternal and child health-care setting, acceptability and proximity of alternative HIV care settings and the burden of HIV infection.

Rationale and supporting evidence

A systematic review found one cluster-randomized trial and three observational studies which showed that integrated services improved uptake of ART and adherence to ART during pregnancy; outcomes for maternal mortality, morbidity, immune response, infant HIV testing uptake and mother-to-child transmission were comparable *(198–203)*. Health-care providers thought that integrated services increased efficiency, decreased waiting time for clients and improved relationships between providers and patients, resulting in less stigmatization and improved adherence to treatment and care *(204)*.

7.9.2 Delivering ART in TB treatment settings and TB treatment in HIV care settings

Recommendation (2013)

In settings with a high burden of HIV and TB, ART should be initiated in TB treatment settings, with linkage to ongoing HIV care and ART *(strong recommendation, very-low-certainty evidence)*.

In settings with a high burden of HIV and TB, TB treatment may be provided for people living with HIV in HIV care settings if they have also been diagnosed with TB *(strong recommendation, very-low-certainty evidence)*.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: summary of key features and recommendations, June 2013 (190)*

Background

The percentage of notified people with TB who had a documented HIV test result in 2019 was 69%, up from 64% in 2018. In the WHO African Region, the WHO region with the highest burden of HIV-associated TB, 86% of people with TB had a documented HIV test result. A total of 456 426 people coinfected with TB and HIV were reported, of whom 88% were receiving ART *(205)*.

Since 2010, WHO has recommended ART for everyone with TB who is living with HIV, regardless of CD4 cell count. In 2021, WHO recommended that ART be initiated as soon as possible and within two weeks after starting TB treatment. Co-trimoxazole prophylaxis is also recommended for all people with both TB and HIV. TB infection control measures are crucial in HIV care settings to minimize the risk of nosocomial transmission of TB.

Rationale and supporting evidence

A systematic review evaluating the effectiveness of delivering ART in TB treatment settings identified 19 observational studies, many of which showed increased uptake and timeliness of ART initiation. However, the data on mortality and TB treatment success were inconsistent. The same systematic review identified five observational studies evaluating the effectiveness of delivering TB treatment in HIV care settings. Two studies reported decreased mortality and another showed comparable mortality rates. The TB treatment success rates and ART uptake were comparable across studies *(206)*.

7.9.3 Integrating sexual and reproductive health services, including contraception, within HIV services

Recommendation (2016)

Sexually transmitted infection and family planning services can be integrated within HIV care settings *(conditional recommendation, very-low-certainty evidence)*.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

Recommendation (2021)

Sexual and reproductive health services, including contraception, may be integrated within HIV services *(conditional recommendation, very-low-certainty evidence).*

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

Among the 1.9 billion women of reproductive age (15–49 years old) worldwide in 2019, 1.1 billion need family planning and 270 million have an unmet need for contraception. Across WHO regions, evidence indicates that sex workers have a greater unmet need for contraception than the general population, and reports indicate excessive reliance on using condoms alone instead of the recommended dual protection *(207–210)*. The proportion of the need for sexual and reproductive health services, including contraception services, that was satisfied by modern methods was 76% globally in 2019, but this fell to less than 50% in western and central Africa. WHO emphasizes the importance of linking sexual and reproductive health and rights and HIV for adolescent girls and young women *(211)*. Since women living with HIV face unique challenges and human rights violations related to their sexuality and reproduction within their families and communities and from the health-care institutions from which they seek care, creating an enabling environment is especially emphasized to support more effective health interventions and better health outcomes *(212)*.

In 2016, WHO conditionally recommended that sexually transmitted infection and family planning services be integrated within HIV care settings *(3)*. Since that time, additional evidence has been published supporting the integration of sexual and reproductive health and HIV. A systematic review published in 2019 that considered linkage and integration found that the proportion of women receiving an HIV test during the study period ranged from 35% to 99% for integrated services and from 20% to 95% for non-integrated services or services integrated at a lower level *(213,214)*; the review summarized findings from several studies that included adolescent girls and young women. The proportion of women accessing HIV services using contraception ranged from 54% to 80% for integrated services and from 10% to 83% for non-integrated services or services integrated at a lower level *(213,214)*. Integrating HIV testing services with sexual and reproductive health services is feasible and has potential for positive joint outcomes. The review included six studies – one cluster-randomized trial carried out in Uganda and five non-randomized cluster trials carried out in Kenya, eSwatini and the

United States of America. Two studies found that integration favoured an increase in sexual and reproductive health services, including contraception; one study found an increase in the uptake of dual contraceptive methods. In the study that reported dual method use, the proportion of women using dual methods during the study period was 34% for integrated services and 0% for non-integrated services *(215)*. The overall certainty of evidence for all outcomes was very low, and the available evidence is limited *(214)*. In the other direction, another systematic review of 14 studies found that integrating family planning into HIV care and treatment settings was associated with higher levels of use and knowledge of modern methods of contraception among women living with HIV *(216)*.

Benefits and harm

Overall, integration is associated with increased offers and uptake of sexual and reproductive health services, including contraception, which is likely to result in improved downstream clinical outcomes. Given the nature of the intervention, the Guideline Development Group considered that the benefits likely outweighed any possible harm. One fear of integration is that tasking providers with too many services may reduce the quality of these services. However, it has been reported that integration can positively affect service quality and client outcomes for contraceptive use, ART in pregnancy and HIV testing *(217)*. Integrating HIV and sexual and reproductive health services has been found to improve accessibility, the quality of antenatal care and nurse productivity while reducing stigma and without compromising the uptake of care *(218)*.

Feasibility, cost and cost–effectiveness

A study from Zambia found that integrated HIV testing and counselling and voluntary male medical circumcision services could be provided at a lower cost per client than segmented, vertical provision *(219)*. A study from Kenya *(220)* found decreased consultation times when services were integrated (10 versus 30 minutes); another study from Kenya *(221)* highlighted the need for sustained systems and health-care worker support over time. Integration may lead to increases in service efficiency, but this is likely to be highly context dependent *(222–224)*.

Equity and acceptability

A survey conducted among health-care providers and clients found that more than 90% of respondents considered that integration is important and feasible. Integration may improve access to sexual and reproductive health services, including contraception, among key populations. A study from Kenya found that access to sexual and reproductive health services, including contraception, for women who inject drugs can be improved by integrating contraceptive and other sexual and reproductive health interventions into existing outreach-based HIV prevention and harm-reduction programmes *(225)*. Another study among female sex workers in Kenya found that integration improved access to the use of non-condom contraception methods, which is important for these people, who may have difficulty negotiating condom use *(226)*. Integration also has the potential to reduce stigma. A survey of health-care providers in South Africa found that they considered integration important for reducing stigma and increasing access to and improving the quality of care *(227)*.

Implementation considerations

Implementing comprehensive and integrated sexual and reproductive health and rights and HIV programmes to meet the health needs and rights of the diverse group of women living with HIV requires that interventions be put into place to overcome barriers to service uptake, use and continued engagement. In all epidemic contexts, these barriers occur at the individual, interpersonal, community and societal levels. They may include challenges such as social exclusion and marginalization, criminalization, stigma, gender-based violence and gender inequality. Strategies are needed across health system building blocks to improve the accessibility, acceptability, affordability, uptake, equitable coverage, quality, effectiveness and efficiency of services for women living with HIV. If left unaddressed, such barriers undermine health interventions and the sexual and reproductive health rights of women living with HIV *(212)*.

Focusing on improving investment in the overall health system is important to support the integration of sexual and reproductive health services, including contraception and HIV services. Laws and policy barriers to accessing sexual and reproductive health services, including for adolescents, need to be addressed *(212)*. Although this applies to any integration effort, it is especially important since sexual and reproductive health programmes have historically been implemented as established vertical programmes within health systems. WHO strongly recommends that care for women experiencing intimate partner violence and sexual assault be integrated as much as possible into existing health services rather than being a stand-alone service *(212)*.

Training on human sexuality may facilitate greater understanding of sexually diverse communities, especially people identifying as lesbian, gay, bisexual, transgender, queer or intersex (LGBTQI) and adolescents and young people seeking accurate sexual and reproductive health and rights information and services *(67)*.

Since an increasing proportion of people living with HIV are receiving their HIV treatment through a differentiated service delivery model with extended ART refills and less frequent clinical visits, aligning the provision of sexual and reproductive health services, including contraception (WHO recommends providing one year of oral contraception and supports community delivery and self-management) and commodities, with differentiated service delivery for HIV treatment models should be considered.

Careful planning and coordination are important for both programme management and service delivery, including establishing integrated data systems and providing consistent cross-training of health-care providers. Moreover, political will and significant coordination, collaboration and integration across disease programmes will be important *(228,229)*.

Research gaps

The evidence supporting approaches to integrating sexual and reproductive health services, including a range of contraception, with HIV services is limited. Research is encouraged to identify approaches to integration that lead to better uptake of sexual and reproductive health services, including contraception; such research should also consider integrating cervical cancer screening and human papillomavirus vaccination. Implementation research is encouraged to evaluate different strategies of integration in different health systems and social contexts, including providing contraception in the context of less frequent clinical and ART refill visits. In addition, research into the efficiency of integrating antenatal and postnatal care and differentiated HIV services outside the maternal and child health service delivery may advise on differentiated service delivery. This in turn would support evidence on the best times for transitioning between maternal and child health services and chronic care.

7.9.4 Integrating diabetes and hypertension care with HIV care

Recommendation (2021)

Diabetes and hypertension care may be integrated with HIV services *(conditional recommendation, very-low-certainty evidence).*

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

Low- and middle-income countries are facing an increasing burden of noncommunicable diseases. Fifteen million people 30–69 years old die prematurely from noncommunicable diseases every year, and 85% of these people live in low- and middle-income countries. Diabetes and hypertension are the major cardiovascular risk factors for target organ damage of the brain, heart and kidneys. An estimated 425 million people in low- and middle-income countries currently have diabetes. This number is expected to increase to 629 million in 2045. The prevalence of hypertension in low- and middle-income countries is estimated to exceed 20% *(230)*. Thanks to widespread access to ART, the life expectancy of people living with HIV has improved substantially, and this places them at risk of noncommunicable diseases that are common with increasing age. In addition to the elevated risks from modifiable factors for noncommunicable diseases such as smoking, poor diet and a sedentary lifestyle, people living with HIV have an independent increased risk of noncommunicable diseases (especially cardiovascular diseases, cervical cancer, depression and diabetes) related to HIV itself and to ART-related side effects *(180,231)*.

In April 2019, WHO convened an expert scoping consultation on noncommunicable diseases and mental health conditions with policy-makers, academics and partners from the HIV, noncommunicable disease and mental health communities to review existing WHO norms and policies for preventing and managing major noncommunicable diseases and mental health conditions. Participants identified the need to establish effective approaches identifying for integrating hypertension, diabetes and HIV services *(232)*.

A systematic review identified five studies – two interrupted time-series studies *(233,234)* and three cluster-randomized trials *(235–237)* – and found that integrated models of care that include hypertension or diabetes or multi-disease approaches may increase the number of people controlling both blood pressure and HIV. It also found that offering integrated care was unlikely to alter mortality (RR 0.90, 95% CI 0.79–1.02). The overall certainty of evidence was very low, and the available evidence is limited *(238)*.

Benefits and harm

The Guideline Development Group concluded that offering integrated services for managing hypertension and diabetes with HIV services will have a small benefit and that any possible harm is small and related to increased workload that may affect the quality of services.

Feasibility, cost and cost–effectiveness

The feasibility of integrating diabetes and hypertension care with HIV services may vary based on the setting and health system factors and should be supported at the planning and policy levels. Involving the community may promote increased uptake of diagnostic, preventive, treatment and referral services for HIV and noncommunicable diseases *(239)*. One study found that engaging regulatory authorities early, considering work culture and building the capacity of a robust interdisciplinary workforce were critically important *(240)*. A comparative study in sub-Saharan Africa concluded that multi-disease services can be offered at relatively low marginal cost *(241)*.

Equity and acceptability

Implementing this recommendation may increase access to routine hypertension and diabetes services among those living with HIV with limited access to primary preventive services. The results of a WHO survey conducted to support these guidelines indicate that most respondents considered integrating HIV and diabetes (83%) or hypertension (78%) care to be very important or important. A systematic review reported high acceptability of integrated adherence clubs for people receiving chronic medication for controlling both HIV and noncommunicable diseases *(242)*. Another review found that most people would accept receiving noncommunicable disease services in an HIV care setting. HIV care providers were willing to provide noncommunicable disease services and recognized the potential benefits of doing so but highlighted concerns around space constraints, increased workload, training requirements, supply chain shortages and potential effects on other services as key factors to consider *(239)*.

Implementation considerations

Focusing on improving investment in the overall health system will be important to support the integration of hypertension, diabetes and HIV services. Since an increasing proportion of people living with HIV are receiving their HIV treatment through a differentiated service delivery model with extended ART refills and less frequent clinical visits, aligning the provision of noncommunicable disease commodities with differentiated service delivery for HIV treatment models should be considered.

Careful planning and coordination are important for both programme management and service delivery, including establishing integrated data systems and providing consistent cross-training of health-care providers. Moreover, ensuring political will and significant coordination, collaboration and integration across disease programmes will be important.

Research gaps

The following research gaps were identified: long-term data on the health outcomes of people living with HIV who have noncommunicable diseases, cost–effectiveness data for various models of integrated care and implementation research on optimizing the supply chain. Research can help to define health promotion activities that encourage lifestyle changes and protect against noncommunicable diseases among people living with HIV, who may face stigma and other challenges in receiving health promotion through the usual channels. Research is also needed to inform how hypertension and diabetes care can be integrated with the common differentiated models of service delivery implemented for HIV. Qualitative research can inform the values and preferences of people living with HIV and noncommunicable diseases related to how care is delivered.

7.9.5 ART in settings providing opioid substitution therapy

Recommendation (2013)

ART should be initiated and maintained in people living with HIV in care settings where opioid substitution therapy is provided *(strong recommendation, very-low-certainty evidence).*

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: summary of key features and recommendations, June 2013 (190)*

Background

These guidelines recommend the same ART eligibility criteria for all adults regardless of drug use behaviour. WHO recommends opioid substitution therapy (with methadone or buprenorphine) for treating opioid dependence combined with psychosocial support *(243)*. Opioid substitution therapy should be integrated and administered in conjunction with ART for those who need it. Although some evidence suggests that opioid substitution therapy improves HIV treatment outcomes among people living with HIV who inject drugs, it should not be a prerequisite for initiating or maintaining ART.

Given the high incarceration rates of people who inject drugs, efforts should be made to ensure that ART is available as part of prison health services. Continuity of treatment and care need to be maintained through appropriate referrals when people return to the community.

Rationale and supporting evidence

A systematic review found one randomized trial and three observational studies evaluating the effect of delivering ART in settings providing opioid substitution therapy. Some studies observed trends of improved viral suppression and reduced mortality, whereas others found comparable rates of viral suppression and mortality *(244–246)*. A more recent systematic review provided additional support for the use of opioid substitution therapy, and its integration with HIV services, to improve the HIV treatment and care continuum among people who inject drugs living with HIV *(247)*. A review of qualitative studies found that convenience and the comprehensive nature of co-located care support acceptability but that health system challenges need to be addressed to deliver integrated services *(248)*.

This recommendation supports expansion of ART by delivering the service in settings providing opioid substitution therapy. Opioid substitution therapy should be provided free of charge or covered by public health-care insurance and should be accessible to everyone who needs it, including in prisons and other closed settings. HIV programmes need to continue to work closely with other service providers to ensure successful implementation of this recommendation. Guidance on maintaining effective opioid substitution therapy programmes is available in the WHO *Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations (70)*.

7.9.6 Diagnostic integration

Good practice statement (2021)

Disease programmes, especially HIV and TB, should actively work towards balanced integration of diagnostic services.

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

The aim of universal health coverage and related services is to deliver high-quality people-centred integrated service and care. Universal health coverage also emphasizes a fundamental shift in service delivery such that services are integrated and focused on the needs of people and communities. One intervention that shows promise in helping to achieve these goals is diagnostic integration. Significant unmet testing needs remain across diseases, including HIV, TB and related infections. Programmatic integration (both sharing devices and integrating networks) is a priority intervention within the universal health coverage agenda to optimize the use of limited resources and improve care.

In 2017, WHO developed guidance for countries on the key considerations of multi-disease testing *(249)*. In 2019, WHO held a country consultation to share experiences and focus on some of the aspects to diagnostic integration *(250)*: funding and resources; optimizing and mapping the diagnostic networks; integrating systems; and considerations related to patients.

Several countries across WHO regions are already moving forward with diagnostic integration. Some countries are also sharing devices and considering integrating HIV and TB diagnostic services and incorporating hepatitis C virus, human papillomavirus and emerging outbreak infections. Several technologies exist that can conduct multiple tests on their technology and can be considered for diagnostic integration or device sharing *(251)*.

Numerous country pilot projects are ongoing or completed, including from the Central African Republic, the Democratic Republic of the Congo, India, Malawi, Mozambique and Zimbabwe. During the 2019 consultation on diagnostic integration *(250)*, countries reported the overall benefits diagnostic integration provides for all health programmes:

- more efficient and comprehensive patient care pathways;
- increased access for underserved or underfunded programmes;
- a more optimized and collaborative integrated diagnostic network with improved laboratory workflow;
- broader device footprints through shared technologies;
- overall, more efficient laboratory services, including data management, sample transport, quality assurance, service and maintenance and supply chain;
- increased negotiating power with suppliers because of increased volumes and a stronger voice for lower, more inclusive, transparent and fair prices across programmes, countries and regions and reduced costs and more efficient use of limited resources by sharing operational costs;

- shared operational knowledge across programmes;
- streamlined diagnostic capabilities and approaches across stakeholders; and
- encouraging integrated cross-sectoral approaches to high-quality testing services and care.

Priorities may have to be set among patients and tests to consider the utilization needs of all programmes and to continue to ensure that the host programmes in particular have full access to device capacity. To ensure more rational integrated testing, several countries have continued testing all people with presumptive TB, with the addition of infant HIV diagnosis and targeted HIV viral load testing; HIV volumes were generally small and ensured no overutilization. Careful consideration for test volumes across diseases and how to set priorities among patients for point-of-care and laboratory referral testing will be critical through network optimization and mapping exercises.

The following challenges have been identified through pilots and programmes.

- Focus is required to adjust the laboratory and clinic workflow on implementing additional assays on the integrated platform.
- Systems considerations need to be implemented to ensure that results are returned on the same day, especially for more urgent tests and results, such as infant HIV diagnosis.
- Adequate human resource capacity is needed to manage additional patient demand.
- Service and maintenance contracts are often limited or challenging (this was specific to the technology implemented during pilot projects).
- Significant support is necessary to ensure that adequate infrastructure is introduced.

Access to high-quality diagnostic testing should be continually expanded across testing needs, ideally combining laboratory-based and point-of-care technologies in an integrated diagnostic network without creating dependence on any one technology. Attention should also be paid to human resources, supply chain, quality assurance, monitoring and reporting and national regulatory components to develop sustainable and strong integrated networks. Careful planning and coordination are important for both programme management and service delivery. Moreover, ensuring political will and significant coordination, collaboration and integration across disease programmes will be important. Further, diagnostic integration and device sharing provide several potential mechanisms to reduce costs across assays, diseases and programmes *(250)*.

Sharing costs between programmes could translate into cost savings for all programmes and more efficient use of resources. Costs can be shared between the host and beneficiary programmes under different allocation scenarios (such as by testing volumes, by allocating entire cost items to each respective programme or by accounting for already incurred investments). Costs are mainly saved by sharing device costs and service and maintenance costs *(252)*. Leveraging existing device fleets with available capacity is a feasible approach to increase access to testing in a cost-effective manner. Tools exist to support countries in understanding the savings available and determining the most efficient and effective strategy.

A systematic review *(253)* found two observational studies reporting outcomes of integrating HIV and TB testing – one conducted by Médecins Sans Frontières in Zimbabwe *(254)* and another by the Clinton Health Access Initiative in Malawi and Zimbabwe *(255)*. Both studies reviewed how integrating HIV testing with TB testing affected TB testing, the programme that procured and set up the technology.

Even with the addition of HIV infant testing and targeted HIV viral load testing, TB testing volume accounted for about 60% of the total after integration. Despite the increase in overall testing volumes, device use never exceeded 75%. Integration with HIV testing did not adversely affect the turnaround time for results or the outcomes. The time to return results and the proportion of people initiating TB treatment were the same before and after infant diagnosis testing and targeted viral load testing were added.

After integration with the TB-procured devices, HIV infant diagnosis and targeted HIV viral load testing experienced more rapid turnaround times and increased treatment initiation rates and increased probability of clinical action for infants living with HIV and people living with HIV receiving ART experiencing viraemia. Offering TB, HIV infant diagnosis and targeted HIV viral load through integrated testing increased device use without exceeding capacity or affecting TB services. Finally, these studies show that integrated testing was operationally feasible, with appropriate site selection to balance the expected demand. TB testing and treatment continued to be provided at the same rate.

Based on the available evidence and country experience, the Guideline Development Group determined that a good practice statement was indicated, since integrating diagnostic services across disease programmes is anticipated to result in a net overall benefit. The Guideline Development Group agreed that programmes should consider integrating their diagnostic services both for programmatic reasons and to ensure comprehensive care for people living with HIV. Increased efficiency is expected, and diagnostic integration and sharing of devices would enable more integrated health services and diagnostic networks.

Anticipated benefits include the potential to improve access to testing by increasing the device base; leveraging programmes' knowledge; and shared operational costs. Diagnostic integration is also expected to create a more optimized, efficient network across diseases, improve patient care and reduce the costs generated in vertical programmes. Diagnostic integration is also expanded to ensure a more robust and reactive diagnostic network, especially positioned to respond to outbreaks and pandemics as they arise.

Knowledge gaps were identified that could benefit from further research, including measuring the impact of diagnostic integration across disease types (including HIV, TB, hepatitis, sexually transmitted infections, cervical cancer and disease outbreaks). Implementation research would be beneficial to generate best practices for diagnostic integration and quality assurance approaches for sustainable delivery of diagnostic integration.

7.10 Delivering HIV services to children

Background

Since 2016, WHO guidelines have recommended initiating ART for all children living with HIV regardless of CD4 cell count and clinical stage. However, gaps along the continuum of care translate into poor clinical outcomes for children living with HIV. Children with HIV are not being identified or are identified late, and even after diagnosis, linkage to care and ART, retention in care and viral suppression are low. The proportion of children lost to follow-up is estimated to be 9–14% during the first year of treatment and up to 28% during the second year of treatment *(254)*. Predictors of attrition included younger age, shorter duration on ART and severe immunosuppression *(7)*.

Several studies have described barriers to access to HIV services by children across the continuum of care. Some barriers are cross cutting, recurring at various stages along the continuum, some barriers are age specific and others are common to all age groups.

Box 7.5 Barriers to treatment and care

HIV testing *(257–263)*

Laboratory-related barriers include long turnaround time for early infant diagnosis and viral load monitoring results, ineffective transport of early infant diagnosis samples, delays in sample processing, reagent stock-outs, equipment maintenance issues and inadequate staffing. Other service delivery challenges include lack of skills in obtaining blood specimens from infants and other young children, lack of consensus on the legal age of consent for HIV testing and disclosure, health-care workers being unfamiliar with HIV testing and disclosure guidelines for children, lack of training in child psychology, obscurity of health-care worker roles in counselling children and inflexible facility working hours and user fees.

Linkage to care and ART initiation *(264–266)*

Barriers to linkage and ART include poor coordination and linkage between service delivery points, provider attitudes and difficulties with paediatric counselling and lack of health-care worker confidence in initiating ART in children.

ART adherence and viral suppression *(267–273)*

ARV drug palatability, ARV drug side-effects and lack of suitable formulations for children may affect adherence to ART and subsequent viral suppression, and pretreatment HIV drug resistance, unavailability of optimal ARV drug regimens and suboptimal ART dosing affect viral suppression. In addition, poor-quality counselling services, inadequate psychosocial support and lack of health-care worker skills to undertake age-appropriate disclosure all affect adherence. Child-related factors that affect their adherence to ART include fatigue and lack of motivation, forgetfulness, refusal, peer influence and non-disclosure *(153)*.

Retention *(274–277)*

Several factors adversely affect retention, including poor-quality counselling and psychosocial support for children, inadequate health information systems to capture data for children, inadequate contact information, weak follow-up systems to trace children, high health-care worker workload, inadequate clinical and laboratory services for managing children, fragmented service delivery with multiple service points at the facility, lack of task sharing, lack of decentralization and drug stock-outs.

Barriers along the continuum of care

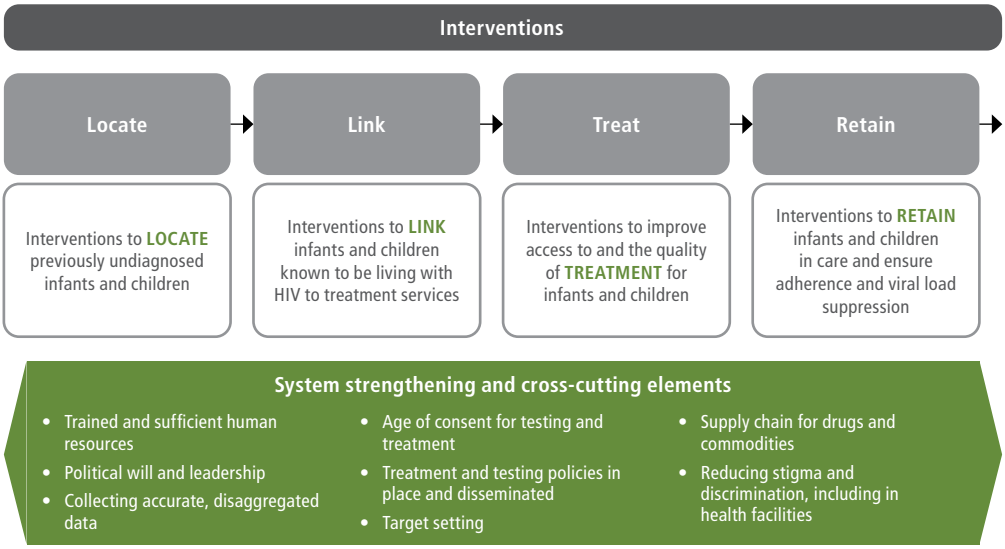
Cross-cutting barriers affecting HIV testing, linkage, ART adherence and retention include lack of child-friendly infrastructure and age-appropriate service delivery, long waiting times at health facilities, physical access constraints for caregivers including distance to facilities, transport costs and time, unavailability of food, fear and stigma among the families of children living with HIV, absence of parents and adult supervision, multiple caregivers with lack of coordination among them, children depending on adults for access, adherence and retention in care, lack of knowledge, caregiver's perception of the child's health and misconceptions about HIV infection among children.

Interventions

These guidelines provide the normative foundation of service delivery models that can improve outcomes among children, including recommendations for: service delivery for children outside the facility; child-centred service delivery; linkage of children from testing to care; rapid ART initiation for children; adherence to ART and retention in care; tracking children and re-engagement in care; task-sharing for child services; decentralization of HIV services for children; and service integration.

Tackling existing barriers and ensure that services for children are scaled up to maximize clinical outcomes requires analysing context-specific barriers to appropriately set priorities among and target a comprehensive set of high-impact interventions along the continuum of care (Fig. 7.2). UNICEF's *Improving HIV service delivery for infants, children and adolescents: a framework for country programming (278)* is a service delivery framework highlighting interventions that improve services along a locate-link-treat-retain continuum and supporting system-strengthening elements and aiming to improve how HIV services are tailored to the epidemic context.

Fig. 7.2 Interventions across the continuum of care



Source: adapted from *Improving HIV service delivery for infants, children and adolescents: A framework for country programming (278)*

7.10.1 Locate and link

With low HIV prevalence among children 0–9 years old in the general population, mass population-based testing is not effective in identifying children living with HIV. Targeted HIV testing focusing on children who have a higher probability of HIV infection is a strategy that maximizes the yield of HIV testing and minimizes missed opportunities for identifying children living with HIV. Integrated approaches that include risk-based screening with validated tools especially for orphaned and vulnerable children *(279,280)*, index family-based testing *(281)*, testing of sick children *(282,283)* and point-of-care early infant diagnosis testing *(284)* would be critical. Chapter 2 provides details of the specific recommendations for HIV testing.

HIV testing of the biological children of index adults and biological siblings of index children diagnosed with HIV or in HIV care should be given priority. Identifying the most appropriate and acceptable setting for index family–based testing either at facilities or in the community will be important, providing appropriate disclosure and psychosocial support with linkage to ART for newly identified children living with HIV.

Strengthening existing infant testing systems for efficient and timely identification of children living with HIV is a priority. Where feasible, point-of-care early infant diagnosis technologies that are strategically positioned within the system, such as at high-volume facilities, and mechanisms for extending services to facilities in proximity can potentially improve the timely detection of HIV infection among infants with early linkage to treatment and care. Facilities providing point-of-care testing must have trained human resources and equipment maintenance and quality assurance measures in place. Alongside early infant diagnosis, continued efforts to strengthen testing beyond the early infant diagnosis time points with rapid testing later in childhood need to be emphasized to address the gaps in identifying older children that constitute the bulk of children and adolescents younger than 15 years living with HIV.

Robust client data management systems (and if possible, electronic systems) are essential to facilitate the tracing of children. Tracking mechanisms (phone call, text messaging, standard mail, email and in-person tracing including using peer models such as mentor mothers) can support the identification and follow-up of mother–baby pairs and the siblings and children of index clients for early infant diagnosis, family and index client testing and linkage to treatment and care.

A key step to targeted HIV testing is assessing risk using simple, context-specific screening tools with high sensitivity and specificity to identify children at high risk of HIV infection. The tools should be easy to administer by higher- and lower-level cadres. This requires standard operating procedures on implementing risk screening and procedures that link screening to HIV testing in specific documentation tools to be developed. A systematic review and meta-analysis of prospective and cross-sectional studies found that current screening tools have only moderate sensitivity and specificity and miss many children living with HIV in high-prevalence areas *(285)*. Screening tools with high sensitivity and specificity therefore need to be developed since this is critical to correctly identifying children at high risk of HIV infection.

Alongside these efforts, it is important to ensure that health-care workers and lay workers are trained and supervised to implement the following:

- targeted provider-initiated testing and counselling with rapid linkage to ART for all sick children in inpatient wards and those attending outpatient, TB and nutrition clinics;
- family-index testing using standardized modalities for tracing children, engaging family members, family HIV testing in different settings, psychosocial support and linkage services both at facilities and in communities;
- risk assessments as an integral component of the HIV testing algorithm for children; and
- providing disclosure support.

7.10.2 Treat

Delay in initiating ART among children leads to increased morbidity and mortality. Early ART initiation for children living with HIV is a priority. Currently, HIV management remains largely physician-intensive, concentrated at higher-level health facilities and centres of excellence, limiting access to services. HIV treatment and care for children has been shown to be feasible in primary health-care facilities with increases in enrolment in care and ART initiation. However, children younger than two years are less likely to initiate ART in primary health care *(286)*. WHO recommends decentralizing HIV services, including ART for children, to primary health-care facilities. To further improve access, early retention and timeliness of ART initiation, WHO also recommends initiating ART outside health facilities, rapid ART initiation (in the case of advanced HIV disease) and same-day ART initiation (if ready) for children. Although a foundational enabling environment that promotes treatment adherence and retention of children is preferred, pre-existing social barriers should not delay initiating ART but rather be addressed alongside ART through tailored and timely supportive interventions (peer counselling, psychosocial support and other services for vulnerable children).

Training, mentoring and supervising health-care workers and lay workers at primary health-care facilities and in communities will be critical to provide a high-quality comprehensive package of services using child-friendly service delivery approaches (including ART initiation and monitoring, caregiver education, disclosure and psychosocial support, adherence counselling, early childhood development and links to other services for vulnerable children) and clear referral mechanisms when further clinical and social services are needed. Case management by mobile phone (mHealth), tele-health and mobile teams are avenues through which higher-cadre clinicians can provide support to health-care workers and lay workers in primary health-care facilities and in the communities to build service delivery capacity and support the decentralization of services.

To date, decentralizing HIV care for children to lower-level facilities has been slow, with limited evidence of the outcomes of children receiving ART at primary health care facilities or outside health facilities. Evidence on the outcomes and effectiveness of decentralized HIV care for children is needed for scale-up. The evidence supporting case management by mobile phone (mHealth), although promising, is still in the early stages *(287)*. Further research on its applicability and impact on children's health outcomes in various contexts needs to be carried out.

Chapter 4 provides the recommendations for ART initiation for children, and section 7.8 provides recommendations for decentralizing treatment.

For child-friendly service delivery, see UNICEF's *Improving HIV service delivery for infants, children and adolescents: a framework for country programming (278)*.

7.10.3 Retain

Several approaches support the retention of children in care, including peer support, such as mentor mothers; home-based adherence and psychosocial counselling; appointment systems; mobile SMS reminders; point-of-care viral load monitoring; community-based services; and differentiated service delivery. All contribute to reducing attrition and improving ART adherence and viral suppression *(288–290)*.

Policies for community service delivery and differentiated service delivery approaches for children that define eligibility, the building blocks (what, when, who and where) in different contexts, guidelines for monitoring children in differentiated service delivery models and criteria for referral will enable these approaches to be scaled up for children, improving adherence and retention in care.

In addition, investing in the training, mentoring and supervision of health-care workers, lay workers and peer service providers to deliver relevant high-quality comprehensive service packages (including clinical components, adherence and psychosocial support) at facilities and in communities that are tailored to the needs of individual children is fundamental. Engagement of community actors, including caregivers, community leaders and community-based organizations, may be considered to support stigma reduction efforts, enable community delivery and encourage sustainability.

Section 7.11 provides details on recommendations for community and home-based adherence and psychosocial support.

Differentiated service delivery

Children who are established on ART are eligible for differentiated service delivery (see the WHO criteria for determining whether a child has been successfully established on ART in section 7.3). Differentiated service delivery for children, although child-centred, should be harmonized with differentiated service delivery for their caregivers in a family-centred approach. The following table summarizes the guidance for differentiated service delivery for children 0–9 years old.

There are several models for differentiated service delivery for children, with wide variability in implementation, including multi-month refills, flexible hours, family clinics and community models. An innovative model is virtual case management or virtual support, especially for caregivers and families who have access to telecommunication services. Robust evidence of long-term retention and viral suppression among children is needed as well as streamlined guidance on eligibility criteria and implementation.

Section 7.3 provides details of recommendations for differentiated service delivery.

Re-engagement into care

Strategies for actively tracing children who have dropped out of care, standard protocols that ensure rapid follow-up and procedural guidance on the mechanisms, including multidisciplinary approaches to support re-engagement, should be developed. To facilitate this, efforts to routinely obtain consent and accurate contact details for community follow-up from caregivers are essential. Approaches for tracing children include phone calls, text messaging, mail, email and in-person tracing or a combination of these. Upon re-engagement, efforts to support retention of children should be emphasized, including counselling, disclosure, psychosocial support, peer support groups for caregivers and enrolment into appropriate differentiated service delivery models.

Table 7.2 Differentiated service delivery for children

Building blocks	Clinical visits	Medication refill visits	Psychosocial support
When?	• 2–4 years old: every 3 months • 5–9 years old: every 6 months Select times and dates that do not compromise school attendance	• Every 3–6 months No need for more frequent than every three months	• Every 1–6 months The frequency and duration of psychosocial support depends on the child's and/or caregiver's needs. It could be part of the package of support at ART refill visits
Where?	• Primary health care closer to home if feasible • At bigger ART sites if primary health care is not available • Outreach services that provide care for adults	• Primary health care • Outreach services • Home-based ART refills • Community-based organizations	• Primary health care • Outside facility (included in the refilling package or community group supports) • Virtual: if low concentrations of children make support groups unfeasible
Who?	• Nurses • Clinical officers • Doctors	• Nurses • Clinical officers • Doctors • Lay providers	• Nurses • Clinical officers • Doctors • Lay providers • Peers • Psychologists • Social workers • Expert clients, mentor mothers
What?	• Clinical care package: physical examination TB screening, nutritional assessment, immunization • Dosage and formulation checks and adjustment • Lab tests: viral load test every 6–12 months	• ART refill • Co-trimoxazole refill • Adherence check • Disclosure process check-in • Referral check: clear pathway to identify needs for referral to clinicians	• Peer support groups: caregivers and pre-adolescence children • Individual peer support for caregivers • Adherence check • Disclosure process check-in • Referral check

Box 7.6 Differentiated service delivery models for children

The Elizabeth Glaser Pediatric AIDS Foundation carried out a programme and policy assessment of differentiated service delivery models serving children and adolescents implemented in seven countries in sub-Saharan Africa. The models included: multi-month refills, weekend clinics, school holiday clinics, child or teen clubs, family model of care and community-based models. They demonstrated a range of feasible differentiated service delivery models addressing children, but the policy analysis highlighted policy gaps limiting access to differentiated service delivery for children. Several countries lacked policies or guidelines that fully reflected the WHO differentiated service delivery guidance and eligibility criteria, resulting in variation in model structure and implementation, including eligibility criteria *(291)*.

Other documented differentiated service delivery for children experiences include:

- decentralized primary health care with outreach support for children and adolescents 0–16 years old (Zambia) *(292)*;
- Standardized Paediatric Expedited Encounters for ART Drugs Initiative (SPEEDI) *(52)*; and
- family clubs (Khayelitsha, Cape Town, South Africa) *(293)*.

7.10.4 Cross-cutting interventions along the continuum of care

Task sharing

Since 2013, WHO has recommended that trained non-physician clinicians, midwives and nurses can initiate first-line ART and maintain ART *(190)*. In 2016, WHO specified that these recommendations apply to all adults, adolescents and children living with HIV *(3)*. However, programme experience suggests that task sharing has not sufficiently extended to children. Across many settings, doctors continue to initiate treatment, especially for younger children in hospital settings. An evaluation of health-care worker values and preferences in task sharing for initiating and maintaining treatment for children undertaken by the PATA network in 2020 highlighted challenges inherent in task sharing, including complexities associated with advanced HIV disease, suboptimal formulations and dose adjustments that may undermine nurse and midwife competence and confidence. Task sharing is critical and urgent to accelerate ART coverage among children.

This entails revising the regulatory framework and investing in preservice and in-service training on ART for children for nurses and midwives, providing regular clinical mentoring and supportive supervision, remote support (virtual platforms and hotlines), delineating roles and ensuring harmonization across all the cadres and levels of care. Standard operating procedures should provide clear indications, pathways and systems for referral to mid- and senior level cadres such as clinical officers and doctors *(63)*. Evidence for task sharing models in care for children is limited. More evidence on task sharing and the outcomes of children in various contexts needs to be generated to inform policy.

Peer programming

Using peer approaches, especially in programmes for preventing mother-to-child transmission, is a low-cost, effective and acceptable intervention for improving children's health outcomes and timely presentation for early infant diagnosis and retention in care *(294,295)*. Peer programming provides another opportunity for task-sharing. Provided with adequate training, supervision and tools, peers can support health-care workers and facilities to execute tasks, including caregiver education and psychosocial support, adherence support, community delivery of ART and community follow-up. Policies should clarify the roles and responsibilities of peers, consider formalizing them within the service delivery systems and establish mechanisms for retaining these cadres.

Monitoring and evaluation systems should establish task sharing and peer programming indicators specific to children and quality assurance mechanisms that monitor the quality of services provided for children by each cadre against established competency levels and standards developed. Job aids, including dosing charts, caregiver counselling and education guides, should be provided to facilitate task sharing. Section 7.7 provides details on the recommendations for task sharing.

Assisted disclosure

Disclosure enhances adherence to ART, but the emotional and mental effects of disclosure to children vary *(296,297)*. Qualitative data suggest that caregivers need support and counselling on approaching disclosure to children *(298)*. Interventions based on an education model have been used to improve the knowledge and skills of caregivers and health-care workers on disclosure *(299)*. Most countries have policies for disclosing HIV status to children in place. Health-care workers and lay workers should be equipped with adequate skills and aids to support the disclosure process in children and to provide post-disclosure support. Children with adherence issues should be assessed for disclosure status and age-appropriate disclosure planned based on their capacity to understand basic HIV concepts, cognitive development and emotional maturity.

In summary, stronger evidence of high-impact service delivery models for children and their caregivers is needed, tailored to the epidemic context, through robust well-conducted operational research that documents experience of programmes in pilots and scale-up and that builds evidence for the interventions in context to inform implementation and policy.

7.11 Service delivery for adolescents

An effective continuum of HIV care ensures that people are retained as they transition between health-care services and providers. Care transitions may be negatively affected by stigma and discrimination, fear of disclosure to new providers and anxiety or inconvenience resulting from changes in providers, their practice style and location. Examples of such changes include adolescents transitioning from paediatric care to adult care; pregnant and postpartum women transitioning from maternal and child health services to adult care; people transitioning from hospitals to primary care facilities; people transitioning from facility-based to community-based services and people in correctional facilities transitioning to general outpatient care. Effective planning and support are needed to ensure that these transitions occur as smoothly as possible.

7.11.1 Delivering high-quality HIV services to adolescents

Recommendations (2013)

- **Adolescent-friendly services should be implemented in HIV services to ensure engagement and improved outcomes** *(strong recommendation, low-certainty evidence)*.
- **Community-based approaches can improve treatment adherence and retention in care of adolescents living with HIV** *(conditional recommendation, very-low-certainty evidence)*.
- **Training health-care workers can contribute to treatment adherence and improve retention in care of adolescents living with HIV** *(conditional recommendation, very-low-certainty evidence)*.
- **Adolescents should be counselled about the potential benefits and risks of disclosing their HIV status to others and empowered and supported to determine whether, when, how and to whom to disclose** *(conditional recommendation, very-low-certainty evidence)*.

Source: *HIV and adolescents: guidance for HIV testing and counselling and care for adolescents living with HIV: recommendations for a public health approach and considerations for policy-makers and managers (300)*

Background

WHO recommends initiating ART among in all adolescents (10–19 years old) living with HIV regardless of CD4 cell count or clinical stage of disease. A growing cohort of 1.7 million adolescents living with HIV includes people infected from birth and those who acquired HIV later in childhood and adolescence *(301,302)*. Although health outcome data for this age group remain limited, emerging evidence indicates that adolescents living with HIV are underserved by current HIV services and have lower access to and worse outcomes on ART than older age groups *(303–305)*. Adolescents are at high risk of loss to follow-up both before and after initiating ART, with older adolescents, pregnant adolescents, adolescent mothers living with HIV and adolescent key populations being especially vulnerable *(304,306–313)*. Peer-driven models of care have demonstrated impact on improving health-seeking behaviour and HIV treatment outcomes for adolescents living with HIV, such as linkage, adherence to ART, retention in care and viral suppression *(314–316)*.

Rationale and supporting evidence

Adolescents, including those living with HIV, face significant barriers to accessing health services, such as inadequate health literacy, limited ability to navigate health systems, legal requirements for parental or caregiver consent and insufficient resources to pay direct and associated service costs *(317,318)*. Adolescents face significant levels of stigma and discrimination, especially adolescents from key populations, among whom criminalization of behaviour such as sex work, drug use and same-sex activity further perpetuates social exclusion and hinders access to health and support services *(319,320)*. The rapid developmental and social changes that occur during adolescence exacerbate the impact of such barriers and can profoundly affect how adolescents engage with health services *(321)*.

Poor-quality services also limit adolescent engagement in health care. Adolescents often perceive health services as unacceptable because of concerns about confidentiality and negative attitudes of health-care providers *(319,320,322)*. Services are often not organized

to accommodate adolescent needs and routines and have inconvenient service schedules, inflexible appointments and unwelcoming environments *(320,321)*. Without sufficient attention and support, adolescents can be lost between services for children and services for adults.

Because of their specific needs, adolescents require high-quality comprehensive services and care to support access, retention and adherence. This includes psychosocial support, sexual and reproductive health and mental health care *(321,323)*. The principles of adolescent-friendly health services are outlined in the WHO-defined characteristics of adolescent-friendly health services (Box 7.7) *(322,324)*.

Box 7.7 WHO-defined characteristics of adolescent-friendly health services

Equitable: All adolescents, not just certain groups, are able to obtain the health services they need.

Accessible: Adolescents are able to obtain the services that are provided.

Acceptable: Health services are provided in ways that meet the expectations of adolescent clients.

Appropriate: The right health services that adolescents need are provided.

Effective: The right health services are provided in the right way and contribute positively to the health of adolescents.

A systematic review *(3)* was undertaken to assess the effectiveness of adolescent-friendly health services for adolescents living with HIV compared with the standard of care. Because of the limited evidence available, the review was expanded to include adolescents and young adults up to and including 24 years of age. Adolescent-friendly health services were defined according to the WHO characteristics and the global standards for high-quality health-care services for adolescents. Eleven randomized controlled trials *(325–335)* and eight observational studies *(336–343)* from four of the six WHO regions were identified. Four studies focused on adolescents living with HIV; the remainder focused on sexual and reproductive health, HIV prevention, mental health, diabetes, general health and smoking cessation. All studies included two or more of the WHO characteristics and global standards for high-quality health-care services for adolescents. Only one study included all WHO characteristics, and no study addressed all global standards.

Adolescent-friendly health services, approaches and interventions compared with standard care showed small but significant improvements in various outcomes, including health outcomes (lower pregnancy rates); health care utilization (presentation at a clinic for mental health, HIV counselling and testing and outpatient visits); uptake of services (HIV testing); knowledge (acquiring HIV and sexually transmitted infections, preventing pregnancy and sexual health); attitudes (towards sex and HIV testing); sexual risk-reduction behaviour (condom use); self-efficacy (condom use or diabetes management); and service acceptability. Outcomes related to healthy lifestyles and quality of life did not differ. Among young people living with HIV exposed to adolescent-friendly health services compared with the standard of care, there was improved short-term viral suppresion and long-term ART adherence. The overall certainty of evidence is low. The Guideline Development Group made a strong recommendation despite low-certainty evidence, citing the promising improvement in outcomes and the existing programme experience, evidence of feasibility and acceptability by the end-users *(3)*.

Cost and cost–effectiveness

A cost modelling study and a retrospective cost analysis for adolescent-friendly health services in low- and middle-income countries reported that, although additional resources are required to ensure the delivery of high-quality adolescent-friendly health services, investments to implement and scale up these services – especially services providing multiple interventions – appear to have value and impact for adolescents *(344,345)*.

Equity and acceptability

Adolescent-friendly approaches aim to ensure that all adolescents obtain the health services that they need, that policies and procedures are in place to facilitate the provision of health services to adolescents and that all health-care providers treat adolescents with equal care and respect regardless of HIV status or risk behaviour.

A global consultation of 470 young people living with HIV and a situational analysis of more than 200 facilities in the WHO African Region was undertaken *(320,346)*; additional input from two unpublished multicountry longitudinal qualitative studies with 147 adolescents living with HIV was also considered *(3)*. Key themes and suggested strategies for improving service delivery focused on empowered and solution-oriented information and support; opportunities for open and honest discussion; skills development on sexual and reproductive health and HIV disclosure from an early age; comprehensive care that addresses issues beyond HIV, including support for adolescents from key populations; flexible scheduling of clinic visits to accommodate school hours; services free of charge closer to home and community-based; dedicated hours and spaces for adolescents; peer-led interventions and services; and an adolescent-competent workforce.

Further, since adolescents living with HIV are a heterogeneous group with varying needs, expectations, preferences and vulnerabilities, care should be taken to ensure equity in service delivery across the age band, paying particular attention to especially vulnerable adolescents, including those from key populations. Relevant WHO guidance and tools are available to facilitate the equitable implementation of adolescent-friendly approaches and programmes, which should consider differentiated intensity and frequency of services for adolescents *(21,347)*.

Feasibility

Programmatic and facility-level evidence suggests that providing adolescent-friendly health services is feasible. A situational analysis of over 200 health facilities in the WHO African Region found that 35% of facilities were attending to adolescents living with HIV separately from adults and/or children through dedicated schedules, staff and/or spaces *(311)*. A case study of a government ART clinic in South Africa found that providing adolescent-friendly approaches in an HIV service setting is feasible. Although the financial costs were low, consideration needs to be given to ensure the engagement of stakeholders, including adolescents; adolescent-specific training for health-care providers and minimal rotation of providers; and adequate time for planning restructured services. A survey of national HIV programme managers highlighted a lack of appropriately trained health-care workers and the need for greater preparation of health-care services as key challenges in delivering HIV services to adolescents *(3)*.

Experience in Zimbabwe has identified several requirements for scaling up adolescent-friendly HIV services, including a national, multisectoral, coordinated response; adolescent-sensitive policies and guidelines; meaningful involvement of adolescents; training and sustained mentorship of health-care providers; community system strengthening; linking community interventions with health facilities; and a national monitoring and evaluation framework with disaggregation and clear indicators for adolescents.

Implementation considerations

The WHO global standards for high-quality health-care services for adolescents provide an approach to improving the services provided to adolescents *(72)*. Examples of how these standards can be adapted to HIV services are available (Box 7.8) *(316)*. The standards are accompanied by an implementation guide that highlights the necessary steps at the national, district and facility levels to achieve the standards and assessment tools to measure implementation *(72)*.

Box 7.8 Global standards for the quality of health-care services for adolescents and HIV-related activities aligned to the standards

Global standard	Description	Example of activities implemented to attain this standard
1. Adolescents' health literacy	The health facility implements systems to ensure that adolescents are knowledgeable about their own health, and they know where and when to obtain health services	Training of peer supporters, also adolescents living with HIV in HIV prevention, sexual and reproductive health, mental health and life skills Developing job aids on HIV testing, care and treatment, viral load monitoring, adherence counselling and contraceptive information and provision specific to adolescents Peer supporters and treatment literacy staff address HIV knowledge and adherence and the concerns of adolescents
2. Community support	The health facility implements systems to ensure that parents, guardians and other community members and community organizations recognize the value of providing health services to adolescents and support such provision and the utilization of services by adolescents	their caregivers join clubs and are involved in activities both between and within clubs Conducting sensitization sessions within schools to eliminate stigma and promote testing, adherence and retention by school-attending adolescents living with HIV Engaging parents and guardians during caregiver sessions and introducing the services
3. Appropriate package of services	The health facility provides a package of information, counselling, diagnostic, treatment and care services that fulfils the needs of all adolescents. Services are provided in the facility and through referral linkages and outreach	Standard operating procedures developed and implemented to provide standard and simplified information on the available package of services Constitute a ministry-led multidisciplinary mentorship team on capacity-building for the needs of the adolescents

Global standard	Description	Example of activities implemented to attain this standard
4. Providers' competencies	Health-care providers demonstrate the technical competence required to provide effective health services to adolescents. Both health-care providers and support staff respect, protect and fulfil adolescents' rights to information, privacy, confidentiality, non-discrimination, non-judgemental attitudes and respect	Training health-care workers at service delivery points on providing adolescent-friendly health services within an integrated service package Regular meetings, on-site support and mentorship and refresher workshops Peer educator curriculum package and teen club guide for peers and health-care providers to use
5. Facility characteristics	The health facility has convenient operating hours, a welcoming and clean environment and maintains privacy and confidentiality. It has the equipment, medicines, supplies and technology needed to ensure effective service provision to adolescents	Clinic appointment hours specific to adolescents and flexible opening hours outside regular clinic hours, such as evenings or weekends or school holidays to facilitate convenient hours and a safe space for HIV care and psychosocial support discussions Multidisciplinary teams scheduled to provide different services; to refill ARV medicine, conduct viral load testing and counsel clients Develop and adhere to the infection prevention and control policies
6. Equity and non-discrimination	The health facility provides high-quality services to all adolescents regardless of their ability to pay, age, sex, marital status, education level, ethnic origin, sexual orientation or other characteristics	Services provided free of charge with no out-of-pocket expenses Client satisfaction survey performed periodically to get feedback for improvement Involvement of multilayered and multisectoral agencies, including social protection services and the district health team
7. Data and quality improvement	The health facility collects, analyses and uses data on service utilization and quality of care, disaggregated by age and sex, to support quality improvement. Health facility staff members are supported to participate in continuous quality improvement	Develop and implement a monitoring and evaluation framework that clearly defines process and outcome indicators Develop and implement standard data collection tools at the facility level and a reporting template that captures age, sex and outcomes Quality improvement teams to routinely review disaggregated data and brainstorm for solutions with health facility staff and district councils
8. Adolescents' participation	Adolescents are involved in planning, monitoring and evaluating health services and in decisions regarding their own care as well as in certain appropriate aspects of service provision	Implementation of youth advisory groups and processes for design, implementation and feedback on services Peer supporters taking part in relevant health team meetings such as case reviews and advocacy for adolescent-friendly health services Training of peers to be self-health managers, to motivate self and others and to be a source of positive peer pressure to others

The implementation guide outlines further actions to implement the standards at the national, district and facility levels *(72)*.

Adolescent peer-driven models and support are key implementation strategies towards the global standard of adolescent participation. The WHO technical brief on peer-driven adolescent HIV models of care *(316)* provides implementation considerations for adapting and scaling up peer-based, adolescent-friendly models and showcases five best-practice case studies based on country experience. The brief advises that peer support is best implemented alongside: routine assessments to monitor progress and quality; standardized peer counsellor recruitment; orientation, training and mentorship of peer counsellors and other stakeholders; deliberate and differentiated care of peer counsellors and health-care workers; and transition planning for peer counsellors ageing out of the programme.

Additional HIV-specific implementation considerations include:

- integrating HIV services for adolescents living with HIV with other adolescent health services, such as those for mental health and sexual and reproductive health;
- aligning approaches for HIV service delivery with WHO and national adolescent-friendly health service standards, protocols and activities;
- including the implementation of adolescent-friendly approaches in HIV health service supervisory and monitoring systems;
- ensuring training, research and personal development opportunities for health-care providers on adolescent HIV treatment and care;
- engaging service providers, adolescents and other key stakeholders to identify acceptable and feasible activities;
- implementing adolescent-friendly health service approaches in all HIV services accessed by adolescents, including antenatal care for pregnant adolescents living with HIV and adolescent mothers;
- establishing links and referral pathways to ensure a comprehensive continuum of care, especially for the transition from HIV services for children to those for adults; and
- addressing the needs and vulnerabilities of adolescents from key populations *(70)*.

Relevant WHO guidance and tools are available *(71,319,300,348,349–352)*.

Research gaps

Although examples of excellence in adolescent-friendly health services for adolescents living with HIV exist *(317,353–355)*, programmes remain poorly documented, with limited scale, and quality and standards vary widely.

Research should contribute to improving understanding of how to implement adolescent-friendly health services within HIV services at a programmatic level and the cost–effectiveness of these approaches in resource-limited settings. Research on the service delivery needs of adolescents living with HIV should examine the minimum package of care; models of delivery at different service levels, including for key populations and pregnant adolescents living with HIV; integrating sexual and reproductive health into HIV services for adolescents; interventions to support safe disclosure; treatment literacy; interventions to address mental health; and the impact of provider training and peer interventions.

The WHO technical brief on peer-driven adolescent HIV models of care *(316)* advocates operational and implementation research to assess the effectiveness of and best practices within peer support programmes.

Supporting adolescent mental health and psychosocial well-being

Both the aforementioned WHO-defined characteristics of adolescent-friendly health services and the WHO global standards for high-quality health-care services for adolescents *(72,322)* highlight the importance of providing an appropriate package of services that fulfils the needs of adolescents. Almost 50% of all mental health conditions start before the age of 14 years, and up to one in five adolescents experience a mental disorder each year *(356)*. Adolescents living with HIV are at increased risk of mental health disorders, such as depression and anxiety *(356,357)*.

The WHO guidelines on mental health promotive and preventive interventions for adolescents provide evidence-informed recommendations on psychosocial interventions for adolescents 10–19 years old that can be implemented in schools, health-care settings, communities or through digital platforms *(356)* and are relevant within an HIV context.

7.11.2 Psychosocial interventions for adolescents and young adults living with HIV

Recommendation (2021)

Psychosocial interventions should be provided to all adolescents and young adults living with HIV *(strong recommendation, moderate-certainty evidence).*

Source: *Updated recommendations on service delivery for the treatment and care of people living with HIV (63)*

Background and rationale

The 2016 consolidated HIV guidelines detailed the key elements of general care over the continuum of HIV care for people living with HIV *(3)*. However, adolescents and young adults living with HIV face distinct and interlinked challenges as they navigate the health-care system, take on responsibility for managing their own care and treatment and confront issues relating to stigma and disclosure *(316)*. Specific guidance is therefore necessary to ensure that interventions specific to adolescents and young people are identified and evaluated.

Adolescence entails biological, cognitive and social changes. It is a phase in the life-course of increased exploration of identity, vulnerability and experimentation, and navigating this phase can be especially complex *(358)*. Adolescents and young adults living with HIV experience numerous mental and social issues, including depression, stigma, isolation, difficulties with treatment adherence and retention, sexual risk-taking practices and substance use *(359)*. In addition, evidence indicates that these people are underserved by current HIV services and, compared with adults 25 years and older, have significantly worse access to and coverage of ART, worse suppression of viral loads and a high risk of loss to follow-up both before and after initiating ART *(3)*.

Psychosocial interventions, which adopt psychological, social and/or behavioural approaches to developing skills and knowledge, have been introduced across a variety of sociodemographic settings, but these interventions have not been adequately explored as a whole.

A systematic review assessed the effect of psychosocial interventions on ART knowledge, linkage to care, adherence to ART, retention in care, viral load, sexual and reproductive health behaviour and knowledge and improved transitioning to adult services. Thirty randomized controlled trials of psychosocial interventions for adolescents and young adults were identified *(360)*. Psychosocial interventions improved adherence to ART (standardized mean difference 0.39, 95% CI 0.11–0.68); reduction in viral load (standardized mean difference – 0.26, 95% CI –0.45 to –0.07) and led to increased viral suppression (odds ratio 1.9, 95% CI 1.0–3.8) and undetectable viral load (odds ratio =1.8, 95% CI 1.1–3.1). No undesirable effects were identified. The Guideline Development Group judged the certainty of evidence to be moderate.

The systematic review described the following psychosocial interventions:

- interventions that harnessed motivational interviewing, a collaborative, client-centred counselling style focused on increasing motivational readiness for behavioural change *(361–366)*;
- interventions that involved adolescents and their caregivers: family-based interventions to promote mental health and prevent negative behaviour (such as nonadherence) among adolescents with HIV, which are designed to strengthen communication, problem-solving and negotiation skills for both adolescents and caregivers *(367)*;
- interventions based around peer support and social networks, which are peer-driven interventions involving multiple intervention components to target adolescents and young adults living with HIV and improve outcomes, including adherence to treatment, retention in care and suppression of viral loads *(314,368–370)*; and
- digital means used to introduce new information and deliver behaviour change skills *(371–375)*.

Benefits and harm

Overall, the net effects on adherence and suppression of viral loads were positive. There were no undesirable effects, and the interventions improved adherence and viral load outcomes. The Guideline Development Group judged the benefits to be moderate and harm trivial.

Feasibility, cost and cost–effectiveness

Overall, psychosocial interventions for adolescents living with HIV were found to be feasible to implement *(314,376,377)*. Many studies reported low attrition rates, indicating that interventions were feasible and well accepted *(362,367,378,379)*. The location of the intervention also influenced feasibility, with interventions delivered digitally or at home considered more feasible because of convenience and flexibility *(369,380)*.

Comprehensive training of existing or new personnel and integrating interventions into existing health-care settings were important for successful implementation *(365,381,382)*. Other feasible interventions used existing support networks to improve engagement in care *(368)*.

There is potential for digital interventions and delivering support through virtual platforms *(383)*. There is an opportunity for delivering blended virtual and face-to-face psychosocial support to support access to equitable and wide-scale services.

Information on the resources used and the cost were extracted as part of the systematic review. Short-term increases in the costs of widespread implementation may offset the longer-term economic and social costs of failing to promote the suppression of viral loads for adolescents living with HIV *(314)*. Psychosocial interventions designed to be implemented by lay counsellors or peer mentors are relatively inexpensive *(367,376,378,384)*. Costs may be reduced by using digital strategies for delivery *(371,379)*. The effects of digitally delivered interventions have been identified as being comparable to or even better than those of in-person interventions *(378)*. Conversely, labour-intensive interventions are more costly *(379)*. Training and employing new personnel to deliver interventions also involve costs. The Guideline Development Group judged the certainty of evidence on costs and resource requirements to be moderate.

Equity and acceptability

Psychosocial interventions are likely to improve equity, especially for more vulnerable groups such as adolescent girls and young women, pregnant adolescents, adolescent mothers and key population groups, and in contexts of high youth unemployment and persistent HIV stigma. The systematic review showed improvements in health equity when approaches are introduced to provide structural support and optimize the potential of peer support and networks and when considering gender preferences for psychosocial support interventions *(385–387)*. The widespread provision of psychosocial services enables adolescents living with HIV to have a more equitable chance to benefit from optimal HIV outcomes by ensuring that each young person receives adequate support to enable them to live physically and mentally well with HIV. The Guideline Development Group judged that offering psychosocial interventions to adolescents and young adults living with HIV would probably increase equity.

A global consultation of adolescents and young adults living with HIV was conducted among 388 respondents across 45 countries, supplemented by 10 focus group discussions with 61 adolescents and young adults with HIV across 10 countries *(63)*. There was near universal agreement (95–98% of respondents) that psychosocial support interventions would help substantially across the HIV cascade and a range of outcomes. Psychosocial support was considered critical to both the mental and physical health of adolescents and young adults living with HIV. The findings demonstrate that psychosocial support is desired and preferred and described as being potentially transformative across HIV treatment outcomes (diagnosis and initiating ART, adherence, retention in care, suppression of viral loads, mental health and sexual and reproductive health and rights). The findings show that adolescents and young adults living with HIV want to receive sustained psychosocial support at each stage of the HIV cascade *(63)*.

Adolescents and young adults living with HIV prefer a varied package of psychosocial interventions, but they consider peer support especially important in managing their health. Interventions that focus on strengthening support from trusted family members and health-care workers are also desired.

Another survey was implemented among frontline health-care workers to assess a wide range of service delivery practices, gaps and enablers *(388)*; 324 health-care workers from 30 countries, primarily in sub-Saharan Africa, participated. At each step in the treatment cascade, the health-care workers reported psychosocial issues as major challenges and recommended psychosocial support strategies more than any other type of intervention. The Guideline Development Group found no important variability on preferences and acceptability.

Implementation considerations

A package of services should be considered that is both acceptable and feasible within the context in which they are to be delivered. This package should be differentiated according to the needs and experiences of different subpopulations of adolescents and young adults living with HIV.

Some adolescents and young adults living with HIV may require adaptations to the content and/or delivery of psychosocial programming to meet their needs. These include adolescents and young adults: with disabilities; who are living with mental health conditions or substance use; who are in and out of school; who are orphans; who are members of ethnic minority groups; who are lesbian, gay, bisexual, transgender, queer or intersex (LGBQTI); who are pregnant; and who are living in contexts of adversity such as extreme poverty and/or humanitarian emergencies. In addition, differences in exposure to risks and protective factors depending on age, developmental stage, sex, health status, whether they belong to a key population and context need to be considered.

Evidence supports psychological approaches such as motivational interviewing and cognitive behavioural therapy. Programmes can include goal setting, problem solving, coping skills, healthy daily routines, interpersonal and communication skills, activating social support and other strategies. Interventions can be delivered through a range of delivery modalities and health-care workers, including clinic visits, home visits, support groups (including peer support and groups that link psychosocial support with ART delivery such as teen clubs), social media and telephone contact. These should be fully integrated within the package of clinical services to optimize impact. Facilitators should be able to develop supportive, trusting, non-judgemental relationships, to maximize engagement in programming; this requires investing in ongoing training, supervision and support for facilitators.

Interventions should be implemented in keeping with the global principles and standards for providing high-quality health-care services for adolescents. The highest ethical standards should be maintained, including voluntary participation, confidentiality, privacy and the best interests of each adolescent and young person. Failure to participate should not affect access to ART or other services.

Peer-driven approaches and the participation and engagement of adolescents are necessary facilitators. The meaningful involvement of adolescents and young adults living with HIV in planning, developing, implementing and evaluating interventions may promote the acceptability and uptake of interventions.

Community support and the involvement of parents, guardians, schools, and other community members in programmes may provide important support for programmes and promote their success.

Research gaps

Additional research is required to identify interventions that improve outcomes for different groups of adolescents and young adults living with HIV. Importantly, research is also needed on content and delivery strategies for interventions to involve parents and caregivers, for both younger and older adolescents, to assess the effectiveness of these programmes.

Further research is needed to inform feasible and effective training, supervision and implementation of support models at scale for facilitators of psychosocial interventions, including peer providers.

There is an ongoing need for research and programme evaluation from resource-limited settings on psychosocial interventions for this group, which would be further supported with more data on the costs and cost–effectiveness of interventions that are currently limited. To further inform implementation, intervention studies should aim to include methods to capture and report costs.

In addition, to enhance the comparability of study findings, intervention studies are encouraged to use standardized outcome definitions to report critical outcomes.

Lastly, follow-up beyond the immediate post-intervention period is needed to understand the long-term impact of psychosocial interventions.

7.12 Improving the quality of HIV care services

Background

This section provides guidance for HIV programme managers and health-care providers on improving the quality of HIV care services. It focuses on key principles, approaches and interventions and provides practical examples of quality assurance and quality improvement practices. HIV programmes should not limit themselves to the examples provided but rather should seek innovative and locally sustainable solutions that strengthen programme monitoring and routine use of programmatic data to improve the quality of HIV care services.

Quality of care emphasizes that services should be effective in achieving their desired health outcomes and that health-care practices should be people-centred and safe *(389)*. The WHO global guidance on people-centred and integrated health services outlines the quality-of-care strategy and provides an overview of evidence and good practices *(390,391)*. Strategies to improve the quality of HIV care services are needed both at the programme management level and at the health facility and community levels where HIV care services are provided *(391)*. If an intervention is to achieve its desired health outcomes, it should be evidence-based, complexity-informed, of high quality and achieve a level of coverage sufficient to bring desired outcomes to the population level.

Rationale for strengthening quality of HIV care services

Although significant progress has been made towards ending AIDS as a public health threat, with 25.4 million of the 38 million (67%) people living with HIV receiving ART by the end of 2019, many opportunities remain to improve access to health services and optimize the quality of service delivery. Opportunities for improvement span the entire care cascade. Opportunities include increasing access to primary prevention interventions such as PrEP and HIV testing and extending to increased ART access and initiation, supporting retention in HIV care and adherence to ART and increasing access to viral load testing among people receiving HIV treatment. Since fewer than half the people living with HIV (41%) have achieved viral load suppression on ART, the risk of substantial population-level HIV transmission and transmission of drug-resistant HIV remains. Other quality gaps remain that present additional opportunities for important changes and include ongoing elevated HIV incidence and mortality and must be addressed by improving HIV care and treatment programmes to achieve the goals outlined in the United Nations Political Declaration on HIV and AIDS. Finally, equity and human rights gaps exist: key populations remain underserved, experience persistent stigma and discrimination and are subject to criminalization, violence and other human rights abuses *(390)*.

To address existing gaps in HIV care services and reach global targets, HIV programmes should establish and maintain systems for ensuring consistently high levels of quality in service delivery. These systems should exist within national frameworks for universal health coverage and be supported by national quality policies and strategies. Three 2018 publications *(389–391)* highlight the implications of inadequate quality of health care. Each year an estimated 5.7 million to 8.4 million deaths can be attributed to poor-quality health care each year in low- and middle-income countries – a figure that accounts for up to 15% of overall deaths in these countries *(391)*. Inadequate quality of care accounts for more deaths than lack of access to health services and leads to annual economic losses in excess of US$ 6 trillion *(392)*.

WHO's 2016 consolidated HIV guidelines *(3)* put forward the following good practice statements for HIV care services that reflect the broader WHO global strategy on people-centred and integrated health services.

Good practice statements (2016)

HIV programmes should:

- **provide people-centred care that is focused and organized around the health needs, preferences and expectations of people and communities, upholding individual dignity and respect, especially for vulnerable populations, and engage and support people and families for informed decision-making to play an active role in their own care;**
- **offer safe, acceptable and appropriate clinical and non-clinical services in a timely fashion, aiming to reduce morbidity and mortality associated with HIV infection and to improve health outcomes and quality of life in general; and**
- **promote the efficient and effective use of resources.**

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

More specifically, with respect to HIV care serviced and in accordance with the 2016 WHO consolidated HIV treatment guidelines *(3)*, high-quality HIV services should:

- provide people-centred care;
- offer safe, acceptable and appropriate clinical and non-clinical services; and
- promote the efficient and effective use of resources *(393)*.

In additional, HIV services should focus attention on:

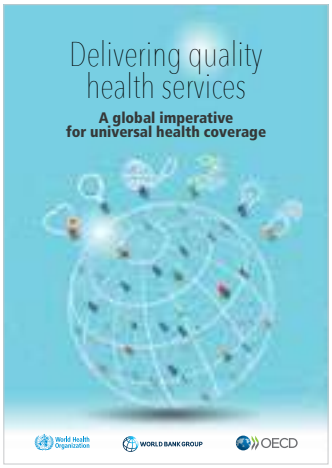
- positive user experiences and attention to the patient voice *(394)*;
- measuring and reducing stigma and discrimination, especially in the health system *(395)*; and
- promoting and sustaining a culture of quality in the programmes and organizations delivering services *(396)*.

WHO technical products on delivering high-quality HIV services

In 2018, WHO published a handbook to support low- and middle-income countries in developing national quality policies and strategies in the context of universal health coverage *(393)* and has published a report with OECD and the World Bank *(389)* that includes a quality call to action (Fig. 7.3).

Within HIV guidelines, WHO has issued recommendations on quality standards *(393)*, high-quality HIV testing *(397)* and improving the quality of HIV clinical services *(3)*.

Fig. 7.3 The quality call to action



Box 6.1 **High-level actions by key constituencies for quality in health care**

All governments should:

- have a national quality policy and strategy;
- demonstrate accountability for delivering a safe high-quality service;
- ensure that reforms driven by the goal of universal health coverage build quality into the foundation of their care systems;
- ensure that health systems have an infrastructure of information and information technology capable of measuring and reporting the quality of care;
- close the gap between actual and achievable performance in quality;
- strengthen the partnerships between health providers and health users that drive quality in care;
- establish and sustain a health professional workforce with the capacity and capability to meet the demands and needs of the population for high-quality care;
- purchase, fund and commission based on the principle of value;
- finance quality improvement research.

All health systems should:

- implement evidence-based interventions that demonstrate improvement;
- benchmark against similar systems that are delivering best performance;
- ensure that all people with chronic disease are enabled to minimize its impact on the quality of their lives;
- promote the culture systems and practices that will reduce harm to patients;
- build resilience to enable prevention, detection and response to health security threats through focused attention on quality;
- put in place the infrastructure for learning;
- provide technical assistance and knowledge management for improvement.

All citizens and patients should:

- be empowered to actively engage in care to optimize their health status;
- play a leading role in the design of new models of care to meet the needs of the local community;

Source: *Delivering quality health services: a global imperative for universal health coverage (389).*

Box 7.9 How does WHO define high-quality health services?

High-quality health services must be:

- effective: providing evidence-informed health-care services to those who need them;
- safe: avoiding harm to people for whom the care is intended; and
- people-centred: providing care that responds to individual preferences, needs and values.

In addition, to realize the benefits of high-quality health care, health services must be:

- timely: reducing waiting times and sometimes harmful delays for both those who receive and give care;
- equitable: providing care that does not vary in quality on account of age, sex, gender, race, ethnicity, geographical location, religion, socioeconomic status or linguistic or political affiliation;
- integrated: providing care that is coordinated across levels and providers and makes available the full range of health services throughout the life-course; and
- efficient: maximizing the benefit of available resources and avoiding waste.

Source: *Why quality universal health coverage? (398)*

High-quality HIV services include the reliable delivery of people-centred clinical care across diverse community and facility settings that are integrated with other services such as maternal, newborn and child health services *(394)* at the national, subnational, district and facility levels. Delivery of high-quality services depends on the strength of an underlying health system foundation and includes optimized management, funding, human resources, information systems, procurement of high-quality pharmaceuticals and devices as well as laboratory supplies and commodities.

National HIV programmes should ensure quality management *(389,390,392,399,401)* through necessary structures, functions and processes to support the delivery of high-quality HIV services.

Box 7.10 Quality management: defining terms

Countries, programmes and organizations use a wide variety of terms to denote systems and processes related to the quality of care. The overview of terms presented here introduces key concepts rather than universally agreed definitions. Indeed, many terms presented here are used interchangeably or may have different connotations in different country or programme contexts. Efforts to address quality should not be hindered by differences in models, approaches or language, and stakeholders should attempt to create a shared understanding of the activities required to improve quality across a system or programme.

Quality management refers to all activities of the overall management function that determine quality policies, objectives and responsibilities and that implement them by such means as quality planning, quality assurance and quality improvement.

- **Quality planning** includes overall quality objectives, priority indicators, governance, organizational structure, selection of health service personnel, allocation of resources, monitoring and evaluation and design and oversight of quality improvement and assurance initiatives.
- **Quality assurance,** in the context of delivery of health services, refers to a range of activities related to systematic assessment and monitoring, intended to ensure that services are fulfilling stated requirements for quality. These include measuring performance against standards; performing external evaluation (such as accreditation); communicating standards to users; and monitoring compliance with established standards. Examples used within HIV programmes include Site Improvement through Monitoring System visits at sites of the United States President's Emergency Plan for AIDS Relief (PEPFAR); site-level assessment of quality indicators; quality assurance checklists for HIV rapid tests; and supportive supervision.
- **Quality improvement** is a specific method designed to continually improve performance as part of a routine process, generally applied by health facility teams within a national quality improvement programme, designed to test changes in programme services, continually measure the effects of these changes and use data to address gaps to improve clinical performance and health outcomes over time.

Sources: *Handbook for national quality policy and strategy: a practical approach for developing policy and strategy to improve quality of care (300)* and Juran & Godfrey *(400)*.

There are numerous definitions of quality-related terms globally in various settings; these were selected in consultation with experts from the HIVResNet Working Group on Prevention of HIV Drug Resistance and Quality of Care.

Quality planning: how should national programmes ensure high-quality HIV services?

1. **Incorporate quality concepts into national HIV policy, strategic plan, strategic information framework and operational and service delivery plans.** The quality of services should be assured at all health system levels, from national programme management to service delivery, within monitoring systems and as part of a continual process to improve health and clinical outcomes (Fig. 7.4) *(3)*.

Fig. 7.4 Enablers of quality HIV services

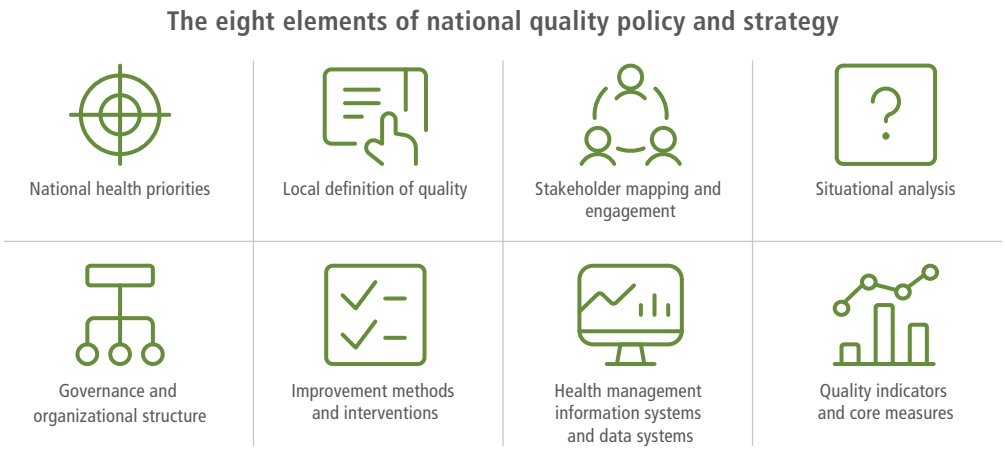
Enablers for quality HIV care services			
Quality HIV care is incorporated into the national policy and programme framework	Quality assurance and quality improvement are integrated into the management and delivery of HIV care services at the health facility and community levels	A defined package of HIV care services is on offer, including which populations and at what level of service delivery	Community engagement for strengthening quality HIV care services; advocacy and demand creation; community literacy on quality

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

2. **Ensure that these elements are supported by a clearly articulated national directives on quality, as described by the WHO** *Handbook for national quality policy and strategy (399)*

   A national quality policy and strategy are organized efforts by a country to promote and plan for improving the quality of care across the health system and support leadership and ownership of high-quality HIV efforts by national health authorities, ensuring integration with both broader national health planning and other disease- or population-specific programmes. The national quality policies and strategies handbook outlines a non-prescriptive approach to developing policies and strategies to support high-quality health programmes and services. The approach includes focusing on eight interdependent elements that help countries to establish their national direction on quality of care (Fig. 7.5).

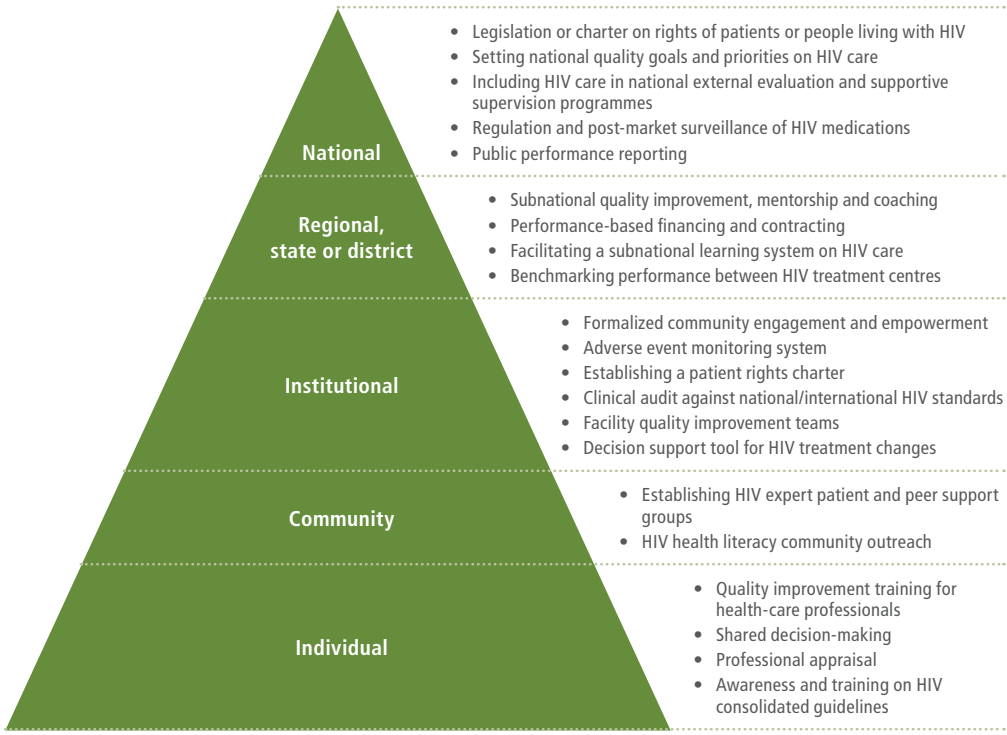
Fig. 7.5 Eight core elements to produce a national quality policy and strategy



Source: *Handbook for national quality policy and strategy: a practical approach for developing policy and strategy to improve quality of care (399)*

Fig. 7.6 illustrates how high-quality HIV services can be considered at different levels; actions to optimize the quality of care are necessary, and possible, at all levels of a health system. However, each country and level should develop its own set of interventions based on local context, need, feasibility, evidence and implementation experience.

Fig. 7.6 HIV quality interventions pyramid: how high-quality HIV services may be considered at different levels



Quality management strategies and frameworks, including those related to reducing stigma and discrimination, provide activities that occur at multiple levels of the health system. These activities go well beyond clinical audits and routine quality assessments and include community-based monitoring. Ideally, quality management strategies should also be considered at a systemic level, including not only different health-care system levels but external factors affecting HIV (such as food insecurity and social inequality). Designing effective, locally appropriate and sustainable quality management strategies requires a shift in thinking from a reductionist, linear approach towards a systemic understanding of the complexity of HIV care. One key characteristic of complex systems is that successful resolution of a problem in one of the elements of a system does not guarantee resolution of core issues. Indeed, a change in one aspect may have unintended negative (or positive) consequences in other parts of the system. Thus, thorough understanding of the complex system, its dynamics and feedback loops is therefore vital to identify points in the system at which interventions are most likely to improve the quality of care and the overall system *(3)*.

Quality assurance: monitoring service delivery standards

Quality assurance is a common term and has different meanings in different contexts. In relation to delivery of health-care services, quality assurance generally refers to a range of activities related to systematic assessment and monitoring intended to provide assurance that services are fulfilling the stated requirements for quality. National quality assurance systems comprise organizations and processes, usually external to health-care providers, aimed at defining, monitoring and improving the quality of care. These may include standard-setting and guideline development bodies, professional registration and licensing boards and external evaluation organizations and programmes. HIV programmes should consider what mechanisms can be used to set appropriate standards, effectively monitor the quality of the services provided, aligning when possible with broader health system approaches to assurance and build accountability into the management of the programme. The 2017 WHO consolidated guidelines on person-centred HIV patient monitoring and case surveillance *(402)* describe patient-level services and indicators across the prevention and care and treatment cascade. Indicators focus on both patient care and management and programme monitoring and management (case surveillance data) use cases. These are anchored to WHO clinical guidelines and may provide a useful starting point for identifying HIV-specific considerations to be integrated within quality assurance tools and systems. The WHO consolidated guidelines on HIV testing services *(9)* provide guidance on quality assurance of HIV testing, and the WHO tool to set and monitor targets for HIV prevention, diagnosis, treatment and care for key populations *(403)* includes quality-related indicators and checklists.

Quality improvement: monitoring performance measures and using data for action

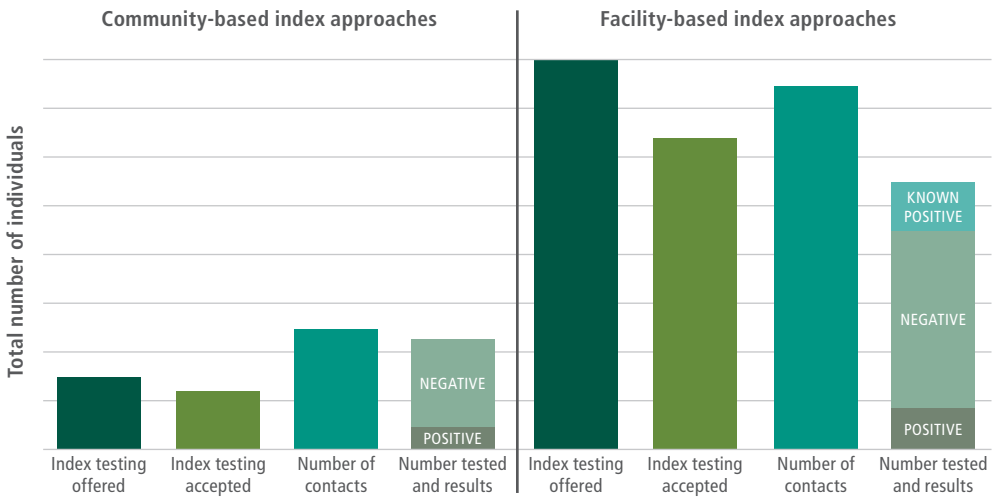
Improving the quality of health-care delivery requires a systematic approach and use of standardized indicators, exploring the root cause of selected gaps in service delivery and leading to designing and implementing contextually appropriate solutions whose impact is subsequently assessed *(404)*. Implementing quality improvement initiatives requires robust data collection, reporting and using indicators. Interoperable information systems (such as client-level and aggregate) help to measure the quality of services, fill gaps in knowledge and communication to end-users, such as district health management teams and facility-level quality committees. Many HIV programmes currently use quality improvement methods that are selected based on available local capacity, resources and the availability of relevant

tools and experience. Regardless of preferences about which model to use, HIV programmes seek to institutionalize a culture of quality improvement and build the necessary capacity for improvement across all levels.

Quality improvement involves the combined efforts of a variety of stakeholders to make changes that will lead to better programmes and systems and ultimately improve health outcomes (Fig. 7.7). There are many quality improvement models, including the model for improvement *(405)*, Six Sigma, lean, total quality management and others. Many of these models use the plan-do-study-act cycle, which is used to continually improve health system performance *(406)*.

The 2015 WHO consolidated strategic information guidelines for HIV in the health sector *(407)* present a framework based on the 90–90–90 targets and include prevention, care and treatment indicators recommended for routine reporting from the service delivery (facility or community) level to the central level, with a subset designated for global reporting. The specific set of indicators of the quality of services selected by a country depends on several factors. Whenever possible, approaches for measuring the quality of HIV services should be integrated with national quality measurement systems and provide disaggregated analysis by sex, age and specific key populations, such as pregnant women, men who have sex with men, people who inject drugs, female sex workers or people living with HIV who have TB, and the 90–90–90 indicators and others can be used to perform cascade analysis to identify programme bottlenecks and frame a set of linked indicators to assess and improve performance (Fig. 7.8).

Fig. 7.8 Cascade analysis for HIV testing services and index testing



Source: Katz et al. *(408)*

The Monitoring and Improvement subgroup of the HIVResNet Working Group on Prevention of HIV Drug Resistance and Quality of Care gave priority to including patient experience indicators in national quality improvement frameworks. In addition, the 2018 report by the Lancet Global Health Commission on High-Quality Health Systems on the Sustainable Development Goals era *(392)* highlighted positive user experience as a key component of high-quality health services, proposing illustrative indicators. Patient-reported experience indicators *(409)* such as avoidance of health care among key populations because of stigma and discrimination are of key importance.

The WHO standards on maternal and newborn care *(396)* include standards reflecting communication and dignity (Standards 4 and 5) that can be considered for HIV programmes. Further efforts are required to capture such dimensions of the quality of services as compassion and patient experience *(392)*, and WHO is working on standardizing associated methodological approaches. Finally, indicators reflecting the engagement of communities and demand-side factors are also important. These may include the satisfaction with clinical services of the recipients of care but also address community perceptions and values around what constitutes high-quality health care, which may vary in different settings and cultures.

Operationalizing national quality policies and strategies within HIV programmes

In many countries, HIV programmes already have well-established quality management processes, offering (1) an opportunity for integration with efforts in national quality policies and strategies, (2) opportunities for HIV programmes to be the pathfinder for national quality policies and strategies (bringing experience, lessons and a foundation for initially rolling out the strategy) and (3) entry points for strengthening the national system for quality of care.

Monitoring as a vital role for communities to improve quality of care

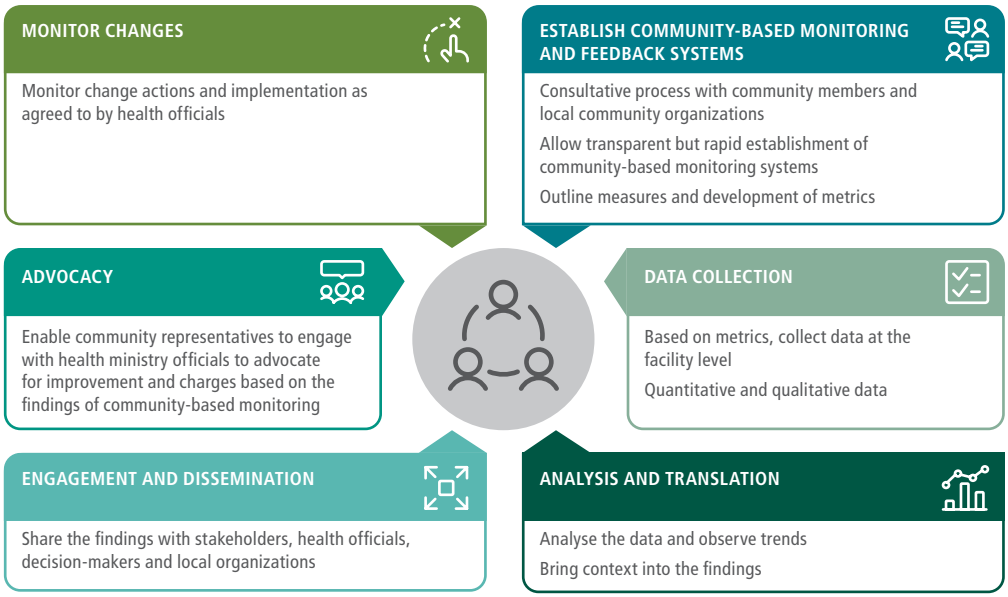
Community-led monitoring is one tool from the array of community-led interventions that people living with and affected by HIV can contribute. Community-led monitoring and consequent advocacy is a central tenet of quality improvement processes for health-care services that enables recipients of care to assess the quality, effectiveness and accessibility of health programmes and services. Community-led monitoring places the recipient of care at the centre of monitoring and advocacy and is implemented using various approaches led by communities in collaboration with other key stakeholders. It can be conducted by independent, local community organizations or a committee of community representatives at the local, national, regional and global levels.

The foundation for effective community-led monitoring and advocacy is HIV prevention and treatment education. When communities are aware of and fully understand prevention, treatment and care standards, they are able to determine indicators that are most appropriate and relevant to track over time. Communities then gather quantitative and qualitative data and observations of health service implementation and uptake aimed to assess the acceptability, availability and accessibility of services. The process must be routine and implemented at least semiannually, in collaboration with local health-care officials. The goal is to enable recipients of care to provide structured input on health-care services, based on evidence and experience, through a collaborative and solutions-oriented process.

The metrics of assessment and feedback must be tailored to the health-care needs identified by local communities. Through a consultative process, the communities support the development of the metrics, measures and tools to be used for community-led monitoring and advocacy.

There are five parts to community-led (or community-based) monitoring: data collection, analysis and translation, engagement and dissemination, advocacy and monitoring (Fig. 7.9).

Fig. 7.9 Five steps of the community-based monitoring cycle



Source: *Community-led monitoring of health services: building accountability for HIV service quality (410)*

Examples of community-led monitoring models range from suggestion boxes and client satisfaction surveys to health facility committees and comprehensive community treatment observatories. Feedback mechanisms ideally are present at each service point or health unit rather than being centrally located in larger facilities such as hospitals. The collective health-care staff should routinely review feedback, and the importance of visibly addressing concerns must be reinforced. Community-led monitoring and routine, active patient feedback mechanisms enable patients to take ownership of their health-care services and gives them a voice in the standards, availability and accessibility of services provided to them.

Through routine and structured community-led monitoring, communities are empowered to contribute to optimizing local health care structures. Community-led monitoring and related advocacy engenders accountability of service providers and local and national officials to standards of high-quality health care, including the availability and accessibility of services; such accountability leads to improved health outcomes *(411)*. HIV multilateral donor and normative agencies (PEPFAR, Global Fund to Fight AIDS, Tuberculosis and Malaria, L'Initiative and UNAIDS) have increasingly acknowledged the importance of community-led monitoring and the related advocacy and have required recipient countries to include community-led monitoring in costed workplans *(411,412)*.

Sustainability

HIV programmes need to implement and sustain quality management systems, especially in the context of wider universal health coverage and national quality policy and strategy efforts to reduce morbidity and mortality from HIV and reach the 95–95–95 targets, Sustainable Development Goals and targets and ending AIDS as a public health threat by 2030. Existing quality improvement efforts have been shown to positively affect clinical outcomes but will require commitment of resources from health ministries to be maintained. Evidence on the sustainability and cost–effectiveness of quality assurance and quality improvement efforts (as with many global health initiatives) and the expansion of proven interventions to large populations is very limited and often non-existent. Nevertheless, existing practical efforts to introduce a culture of quality awareness can be strengthened, as demonstrated by numerous country examples.

Addressing these requires planning, involvement of health ministries and stakeholders, communities and recipients of care and partnerships with local organizations and donor agencies. Organizational cultures need to be changed as well as local systems and infrastructure, including information systems that collect routine programme data that are both accessible and of high quality. With the current momentum towards high-quality health services and the quality call to action *(413)*, it is time for a quality revolution and to scale up quality management efforts within HIV programmes. This is especially important in the context of universal health coverage and the United Nations High-level Meeting on Universal Health Coverage in September 2019, which included a key call for building high-quality health systems that people and communities trust, in accordance with the quality call for action (Fig. 7.10).

7.13 Procurement and supply management systems for HIV health products

Overview

This section provides operational guidance on procurement and supply management, with a focus on how procurement and supply management systems can respond to new recommendations in these guidelines. Comprehensive advice on the general management of procurement and supply management systems is readily available in existing publications and training materials. References to relevant publications and materials are provided at the end of this section.

The overarching objective of procurement and supply management systems is to support national policy with the adequate and continuous availability of the most effective, heat-stable, fixed-dose, quality-assured ARV drug formulations, diagnostics and other consumables at service delivery sites, in the right quantities, at the lowest possible cost, with the right remaining shelf life on delivery and in a timely manner.

All people living with HIV should be able to initiate ART regardless of clinical stage or CD4 cell count. This requires an integrated national strategic response that considers the resources available and enables strong procurement and supply management systems at all levels of the health system. In addition, the fact that all people living with HIV need to be receiving ART will accelerate the scale-up of ART programmes.

Implementation considerations

Challenges and opportunities associated with implementing WHO recommendations related to ARV drugs and diagnostics include:

- product selection;
- quantification and demand forecast;
- the ability of global supply to cope with increasing global demand;
- procurement planning and execution, including the timeliness of orders and delivery;
- storage and distribution, including logistics constraints;
- monitoring of consumption and demand changes;
- frequency of ARV drug pickup and the flexible algorithm for multi-month dispensing (specific to ARV drugs);
- information flow between stakeholders at different levels;
- costs and opportunities for saving;
- product shelf life;
- risk of stock-outs if product procurement is unaligned with demand; and
- risk of expired health products if the quantities procured have been overestimated.

These issues can be addressed through a national stakeholder working group that would develop a plan to address these issues, with participation that includes health policy-makers, implementers, funders, procurement and supply management specialists, central medical stores management and the finance ministry.

Selecting pharmaceutical and diagnostic products

- Medicines and diagnostic products should be selected in accordance with national guidelines and programme needs.
- National guidelines should provide guidance on using alternative regimens or diagnostic technologies in case of drug toxicity and treatment failure, infrastructural limitations and supply shortages, respectively, in accordance with the WHO recommendation.
- WHO recommends that the overall number of regimens be minimized to optimize treatment and sourcing. According to WHO country surveys conducted in 2020, some countries are using more than 20 ARV drug regimens.
- Before new products are included in national essential medicines and diagnostics lists, registration and intellectual property status should be verified to ensure that the product can be imported.
- If a selected ARV drug or diagnostic is not on the national drug list and/or registered in the country, HIV programme managers should coordinate with the national regulatory authority and request that these commodities be put on the list and properly registered. Pharmaceutical and diagnostic companies have a responsibility to register products in countries where they market their products, and countries have the responsibility to ensure that products desired for procurement are registered.

- To avoid confusion, drugs and diagnostics products no longer recommended by WHO for any ARV drug regimens and removed from the WHO List of Essential Medicines should be removed from the national ART guidelines and essential medicine lists, and plans should be made to transition people to more effective regimens using existing stocks as appropriate. Any remaining stock should be properly disposed of.
- The synchronized introduction of new guidelines with forecasting, procurement and distribution planning will minimize waste associated with products that are being phased out as well as shortages of newly recommended products during the transition process or period.
- Key performance indicators should be developed to monitor drug and diagnostic use as well as wastage and stock-outs.

National essential medicine lists should be optimized for ARV drug formulations for children following the detailed guidance on preferred products for children provided in *The 2021 optimal formulary and limited-use list for antiretroviral drugs for children: policy brief (414)*.

Quantifying and forecasting demand

To determine the volume of products required to meet programme demand, procurement and supply management managers need to know:

- the numbers of people receiving treatment, disaggregated by age group;
- the regimens used by these people;
- the proposed changes in regimens, if any;
- the expected rate of scale-up of treatment: the increase in numbers of people receiving each regimen in a given period of time;
- the number of rapid test kits required to identify people living with HIV in accordance with scale-up targets;
- the forecasted uptake and continuation of PrEP *(415)*;
- the frequency of multi-month dispensing; and
- which products are approved and registered for use in the country.

Similarly, for diagnostics key information would be useful for quantification and forecasting, including:

- the number of people needing testing (separate quantifications will be necessary for each test type: CD4 to identify advanced HIV disease, infant diagnosis and viral load testing for people living with HIV receiving treatment);
- the number of tests required for each population;
- the specific test used for each population and at each health-care facility; and
- the expected rate of scale-up of testing.

The process of quantification of needs can be highly complex. Best practices suggest that the quantification should be undertaken annually, projecting for at least two years, with a semiannual review to ascertain whether any significant upward or downward adjustments are required. Assuming that financial resources are available, procurement and supply management managers can then plan ahead and place long-term orders based on a staggered delivery algorithm while allowing sufficient flexibility to adjust for potential changes in the pace of scale-up, regimen switching and/or other unforeseen events affecting consumption.

When product volume demand for a specified period has been quantified, procurement managers should develop a supply plan that considers:

- the months of stock currently available;
- the existing orders yet to be fulfilled by vendors;
- the budget available for new orders;
- the volume of new products required to satisfy forecasted demand, including provision of a reasonable buffer stock; and
- the required delivery dates for new shipments to avert stock-outs.

WHO recommends that the process of supply planning be undertaken semiannually to accommodate changes in demand and any delivery delays from suppliers.

Procurement

A uniform and harmonized procurement system is required to efficiently procure quality-assured, affordable ARV drugs and diagnostics. Procurement should be based on selection of appropriate products and forecasted needs, considering consumption, expanding services, phasing in and phasing out formulations and implementing new recommendations, including multi-month dispensing. Transparent procedures should be adopted to achieve best-value procurement and a quality assurance system should be implemented to procure, store and distribute quality-assured pharmaceuticals, diagnostics and other health products.

National procurement programmes should:

- request that partners supporting the national HIV programme consolidate procurement and supply management systems to pool procurement for ARV drugs and diagnostics;
- consider joining other pooled procurement mechanisms to access favourable prices negotiated by large buyers and donors to increase economies of scale and minimize the risk of long delivery times observed with small orders (second-line ART and ART for children);
- conform with agreed specifications for selected products to ensure a common basis for procurement competition, quality assurance standards and any special needs such as packaging or identification, with special requirements likely leading to price increases;
- use a competitive process to ensure value for money;
- for commodities in regular and repeated demand, such as medicines and diagnostics, establish or access long-term framework-type contracts between large institutional buyers and manufacturers against which call-down orders can be placed, which will reduce procurement transaction costs and reduce the time elapsing between identifying the need and fulfilling the order and help to build collaborative relationships between buyers (national procurement managers) and sellers (suppliers);
- wherever possible, implement a multi-supplier procurement strategy to support a healthy market and avoid dependence on a single supplier, which will also provide flexibility during periods of supply constraints or where individual suppliers face problems related to access to active pharmaceutical ingredients and key starting materials, in addition to manufacturing, production or logistical difficulties that may lead to delays;
- use a publicly accessible database to facilitate access to information about prices and support competition; and
- follow the principles described in the United Nations interagency guidelines for donated drugs and the WHO Model Quality Assurance System for Procurement *(416)*.

National programmes should be aware that other countries and programmes will be ordering the same or similar formulations and tests, and manufacturers may already have existing orders that would account for the entirety of the manufacturing capacity, possibly for several months ahead. Working with their suppliers, procurement managers will be able to place their orders according to their required volumes and delivery schedules. Advice on manufacturer production capacity and any existing supply constraints and opportunities may also be available from the organizations and contacts provided at the end of this chapter.

Storage and distribution

Appropriate storage and distribution of HIV medicines, diagnostics and other commodities are essential. Recent recommendations that all people living with HIV should be able to start ART, preferably a DTG-containing regimen, take at least one viral load test per year per person, CD4 for staging of HIV advanced decease, increase the use of infant HIV diagnosis and implement the new multi-month dispensing model will significantly increase commodity volumes and the demands on storage and distribution throughout the supply chain and at the patient level. Countries will need to examine the appropriate level in the supply chain to hold stock, plan for new public facilities or examine alternative approaches, including leveraging additional resources by outsourcing to private sector facilities, provided that they are appropriate to store pharmaceuticals and diagnostics. Neither of these options is a quick fix; funds permitting, contracting with private sector providers may take many months to complete the appropriate tendering, contracting and quality assurance of providers before available facilities can be activated for use. Countries may also explore the potential of existing parallel systems, such as cold-chain facilities in immunization programme infrastructure for products that require temperature control.

Procurement and supply management systems should consider planned programmatic changes in service delivery related to the frequency and locations where people receive their ARV drugs. For example, community distribution of ARV drugs to people who are clinically stable and community-based HIV testing and ART start may involve another step in the local supply chain and potentially increase the quantity of ARV drugs and diagnostics to be procured and distributed. Changes that positively affect the amount of stock retained at each level, including by the client, need to consider the shelf life of the ARV drugs. For example, the most common first-line ARV drugs currently have a 36-month shelf life, and many rapid test kits have only a 12- to 18-month shelf life.

Storage and distribution plans should include:

- quality assurance of products on receipt at the warehouse;
- availability of secure storage facilities appropriate for pharmaceuticals and diagnostics;
- cold storage for products that require temperature control;
- rationalization of the number of storage levels to reduce the length of the supply pipeline;
- inventory control systems with appropriate minimum and maximum levels that trigger reordering;
- regular distribution patterns to service facilities, with increased frequency of potentially smaller deliveries supporting more effective use of existing limited space and distribution capacity;
- routine data reporting from facilities to monitor usage and identify changes in predicted consumption patterns that may risk overstocks (which can be reallocated to avoid expiry) or stock-outs; and
- a shelf-life management system.

Ensuring secure supply for programme flexibility and to avoid stock-outs and expired health products

Avoiding stock-outs is essential to prevent treatment discontinuation. Recommended actions to avoid the risk of stock-outs include the following.

- Close coordination with programme managers and policy-makers is required to understand the planned progression towards the "treat all" targets. Programme managers and clinicians should agree on the speed at which new people will initiate treatment, how the treatment outcomes will be measured, how newborn babies will be screened and how people with advanced HIV disease will be assessed to ensure that the required commodities are available. A faster-than-necessary introduction of new people receiving ART will exhaust stocks and cause an increased risk of stock-outs, and a slower-than-planned introduction risks overstock and wastage because of expiry.
- The supply chain implications of any recent or proposed changes in the service delivery model, such as multi-month dispensing or community distribution of ARV drugs, should be clearly understood.
- Ensure that the ARV and diagnostics supply chain – especially its distribution system and allocation of commodities by facility – reflects the geography of the epidemic.
- New recipients should initiate the preferred first-line regimen, unless clinically contraindicated.
- Quantification and ordering should include a rotating safety buffer to compensate for errors in forecasting and potential delivery delays. It is recommended that the buffer be part of normal stock rotation, not a separate stockpile, to avoid the risk of retaining aged or expiring product. The level of buffer may vary but should cover at least one round of planned deliveries so that any delivery delay will not lead to a stock-out. Forecasts should be revisited at least semiannually to adjust for variance between forecasts and actual demand and to review demand for the next 12–18 months, adjusting orders as necessary.
- Orders should be placed in a manner enabling timely delivery. Procurement managers should work closely with their suppliers to understand the suppliers' normal delivery periods and plan accordingly. It is recommended that orders be placed at least 12 months ahead of the required date of delivery, since this will allow adequate time for production and – where volumes allow delivery by sea freight – reduce the cost of shipping. It is also recommended that, where practical, deliveries be staged rather than arriving as a large shipment for six months or more of stock. Staged deliveries enable more flexible delivery schedules and enable procurement and supply management managers to make the best use of existing storage and distribution capacity.
- The procurement and supply management manager should also be aware of potential and actual constraints in the global market. In 2020, there were some constraints in the availability of important active pharmaceutical ingredients. This affected the ability of formulators to manufacture and deliver finished product on time, and, where possible, such inconveniences must be factored into requested delivery times when placing new orders.

- Where possible, special consideration should be given to products with low demand, such as many drugs used by adults or adolescents receiving second- or third-line ART and many ART regimens for children and infant diagnosis. Production of these commodities will be less regular, and many countries only require low volumes, usually less than a full production batch. Pooled procurement at the national level and cooperation between countries and with suppliers may be appropriate for these products, and buffer stocks may need to be higher to compensate for less regular deliveries and challenges in accurately forecasting usage and uptake. Examples of such mechanisms include the PAHO regional drug facility and the Paediatric ARV Procurement Working Group. Countries can also consider placing orders through institutional mechanisms such as the Global Fund's wambo.org platform, which assures the best prices and delivery times.
- Where procurement regulations allow, it is recommended that framework contracts be placed to enable call-down orders. This maximizes the flexibility in delivery schedules that can be adapted to actual consumption and reduces the need for frequent repeat procurement and bidding exercises without compromising value for money.
- Several of the above actions will limit the risks of stock-outs and expired products (such as moving ARV drugs from low-volume treatment sites to high-volume treatment sites). However, when expired products are identified, they should be destroyed according to approaches and various disposal methods outlined in the WHO *Guidelines for safe disposal of unwanted pharmaceuticals in and after emergencies (417)*.

Use and monitoring

Robust information systems ensure the availability of accurate and timely consumption data on drugs and diagnostics and other information required for effectively monitoring the performance of the entire supply system and for forecasting the quantity of ARV drugs and diagnostics needed. Monitoring procurement and supply management by effectively using early warning indicators prevents stock-outs and overstocks, which could lead to expiry. Reliably capturing and analysing usage and consumption data from facilities will support a robust bottom-up approach to quantification and forecasting that will reflect changes in demand and support a flexible approach to introducing new recommendations in these guidelines.

Special considerations for ART regimens for adults

Four key challenges for the supply chain arise as a result of the current recommended ARV drug regimens.

- The currently approved suppliers of fixed-dose combination formulations of TLD are expected to have sufficient production capacity to satisfy the increased demand for these formulations as the numbers of people on treatment increase if increases are carefully phased to avoid sudden spikes in demand. However, short-term supply constraints may arise, highlighting the need for efficiently planning, maintaining and managing buffer stocks at the national level.
- Delivery lead times for the recommended first-line medicines may become extended during peak periods of demand. Procurement and supply management managers should be aware of current lead times and plan their orders and deliveries accordingly.

- Purchasers and implementing partners who are distributing TLE-, TEE-, AZT- and EFV-based regimens to users and have stocks and orders in process should consider how they manage their stocks to avoid stock-outs or wastage from expiry of usable products from overstocks.
- Where demand for certain regimens is limited, pooling orders from several buyers is recommended to increase the volumes to be ordered and to ensure that suppliers can deliver and adequately respond to the demand.

Transitioning to recommended preferred regimens and preferred formulations

Programmes should plan carefully and discuss with their suppliers the pace at which increased quantities of TDF- and DTG-based products can be made available. To ensure that supply is available to meet anticipated demand, a phased programme is highly recommended. The following approaches are suggested.

- Initiate new people living with HIV eligible for ART on DTG-based regimens, with preference for the fixed-dose combinations of TLD.
- Include buffer stocks in supply plans and liaise closely with suppliers, global public sector procurement platforms and the major pooled procurement mechanisms to understand global demand patterns and act accordingly.

Programmes should stop procuring the following.

- d4T, ddI, FPV, IDV, NFV, NVP and SQV should no longer be procured since these are no longer recommended as an alternative NRTI or PI in first or second-line regimens for adults or adolescents because of toxicity, lower efficacy and inconvenient dosing requirements.

People currently receiving first-line AZT- and/or NVP-based regimens should be transitioned to TLD, TLE 400 mg if they cannot tolerate DTG.

In areas with a high prevalence of HIV-2 infection, procuring and using formulations with two-drug fixed-dose combinations (TDF with 3TC, TDF with FTC and AZT with 3TC (in second-line ART) might be a preferred option, since this provides flexibility to combine the NRTI backbone with PIs or INSTIs in first- and second-line therapy for people living with HIV-2 infection.

In the case of newer products such as DTG, DRV and RAL for children or existing products with low demand (such as for second- or third-line regimens), where feasible and practicable, procurement managers should consider pooling their demand with other domestic programmes, neighbouring countries, other regional programmes and/or collaborating with major purchasers to form a part of total orders that meet manufacturers' production batch sizes. Shelf life, storage facilities and consumption patterns permitting, procurement and supply management managers should also plan to hold larger buffer stocks for essential products in low demand. For newly introduced products, initial orders requiring longer lead times should also be assumed.

Supply chain considerations for implementing less frequent ARV drug refills, community ART delivery and lay health-care providers distributing ARV drugs

Programme managers and policy-makers need to consider several supply chain issues when implementing recommendations regarding less frequent ARV drug pickups and/or using community ART delivery service delivery models and lay health-care providers distributing ARV drugs. Procurement and supply managers and policy-makers should examine the current ARV drug supply chain model and its performance to determine the adaptations needed to enable the supply chain to support the achievement of these recommendations. Since one-size-fits-all supply approaches will not meet the needs of differentiated care models, the local supply chain must be agile enough to serve a variety of service delivery models, including at the community level. In addition, programme managers should consider taking a phased approach that considers:

- the additional ARV drugs needed at facility or pickup sites, including providing a safety buffer stock;
- the total number of people to be served by multi-month (3–6 months) prescribing and the regimens they currently use;
- the capacity of local distribution sites to safely, optimally and securely store and manage the additional ARV drugs;
- the additional reporting needed by the logistics information system to track the ARV drugs through these sites, including at the community level;
- any ARV drug shelf-life constraints;
- the overall performance of the supply chain in which the recommendations will be implemented; and
- incorporating additional ARV drug requirements in the country's annual quantification, funding, procurement and supply plans.

Besides the quantity of additional products initially required to implement these recommendations, the manufacturing capacity and lead time may influence the pace at which programmes can take new recommendations to national scale.

Special considerations for ART for children

Given the continuing challenges of ensuring the availability of ARV drug formulations for children, WHO and partners provide guidance on optimal ARV drug products for children to promote a secure and sustainable supply. The group met in December 2020 to revise and update the Optimal Formulary *(414)*. The sixth edition of the Optimal Formulary (Table 7.3) and Limited-use List (Table 7.4) is intended to support the transition and implementation of preferred and alternative ART regimens recommended for infants and children in WHO guidelines across all lines of treatment.

Table 7.3 Optimal Formulary

Minimum number of ARV drug formulations needed to provide all currently WHO-recommended preferred and alternative first- and second-line ART options for infants and children and infant prophylaxis for preventing the vertical transmission of HIV

Drug	Dosage form	Strength	Rationale for use	Pack size
DTG[a]	Tablet (dispersible, scored)	10 mg	For first-line or second-line ART for infants and children who are ≥4 weeks of age and weighing 3 to <20 kg	90 count
ABC + 3TC	Tablet (dispersible, scored)	120 mg/60 mg	For preferred first-line or second-line ART for infants and children weighting 3–25 kg	30- and 60-count packs
AZT[b]	Oral solution	50 mg/5 mL	For postnatal prophylaxis and treatment of neonates (first four weeks of life)	240-mL bottle
NVP	Oral solution	50 mg/5 mL	For postnatal prophylaxis and neonatal treatment only	100-mL bottle
LPV/r	Tablet (heat stable)	100 mg/25 mg	For alternative first-line or second-line ART for children weighing ≥10 kg and who are able to swallow tablets whole	60-count pack
LPV/r	Oral granules	40 mg/10 mg	For alternative first-line or second-line ART for infants and children weighing ≤10 kg or unable to swallow 100 mg/25 mg tablets whole	120-count pack
AZT + 3TC	Tablet (dispersible, scored)	60 mg/ 30 mg	For second-line ART for infants and children weighing 3-25 kg	60 count pack

[a] DTG 50-mg film-coated tablets is the preferred formulation for children weighing ≥20 kg (and co-formulated DTG 50 mg + TDF 300 mg + 3TC 300 mg – also known as TLD – for those weighing ≥30 kg) to reduce the pill burden, simplify supply chain processes and reduce programme costs. Programmes should ensure that the ≥20 kg population is accounted for during quantification for DTG 50-mg tablets.

[b] As of March 2021, AZT oral solution is only available in a 240-mL bottle. This formulation is only anticipated to be used for neonatal treatment or enhanced infant prophylaxis. AZT oral solution has a four-week shelf life after opening, and if infants use AZT oral solution for longer than this period, a new bottle should be issued after four weeks.

Table 7.4 Limited-use List

ARV drug formulations that are included in the WHO guidelines and are needed for a limited time or in low volumes

Drug	Dosage form	Strength	Rationale for use	Pack size
NVP	Tablet (scored, dispersible)	50 mg	Only for postnatal prophylaxis when NVP oral solution is not available	60-count packs
3TC	Oral solution	50 mg/5 mL	Only for treating neonates (first four weeks of life)	240-mL bottle
RAL	Granules for suspension	100 mg	Only for treating neonates (first four weeks of life)	60-count packs
LPV/r	Oral pellets	40 mg/10 mg	For specific circumstances in which DTG 10-mg scored tablets or LPV/r oral granules are not available or clinically indicated	120-count packs
DRV	Tablet	75 mg, 150 mg	For third-line ART regimens for children three years and older	480- and 240-count packs
RTV	Tablet	25 mg	For superboosting of LPV/r with during TB treatment and required for use when administering DRV	60-count packs

To ensure smooth implementation of recommended first-line regimens for children, it is critical for policy-makers and implementers to consider the availability of ARV formulations for children. National programmes are urged to limit the procurement of ARV drug products for children to formulations on the Optimal paediatric Formulary. Complying with the ARV drug Optimal Formulary – which is based on WHO recommendations – will help to simplify the supply chain and aggregate global demand to stabilize the global supply of ARV drugs for children.

Funding agencies, procurement entities, manufacturers, national medicine regulatory authorities and national governments all have a critical role to play in working together to ensure the availability of products on the Optimal Formulary and Limited-use List, which can be achieved by fast-tracking in-country registration, maintaining procurement and supply-chain planning, facilitating commercialization, ensuring manufacturing capacity and filing applications for registration in other countries. Having one or more quality-assured suppliers available at the national level is a criterion for selection of products.

Specific consideration for treatment and procurement for children

When available, age-appropriate fixed-dose combinations for any recommended regimen are preferable.

Dispersible tablets (or granules for oral solution) are preferred formulations for children because tablets or granules can be made into liquid when administering the drug to the child. If suitable dispersible formulations are not available and oral liquids must be used, it is recommended that children be switched to a solid oral dosage form (such as granules, pellets or dispersible tablets) as soon as possible.

Administering ART to neonates generally requires oral liquid formulations, and switching to solid oral dosage form as soon as possible is recommended (for example switch from RAL or NVP to DTG 10 mg scored dispersible tablets at four weeks of age).

Scored tablets are preferred to ensure accurate dosing. Splitting unscored tablets should be avoided since uniform distribution of active drug product cannot be assured and the bioavailability of the drug within the body may be decreased.

Oral liquid formulations should be avoided in favour of solid oral dosage forms when available.

For further guidance to support the transition to new formulations for children see tools and policy briefs in the AIDS free toolkit *(348)*.

Checklist for introducing new products and phasing out old ones

Introduction of new medicinal or diagnostic products is one of the most complex and unpredictable activities in any HIV programme and as such presents a heightened challenge for policy-makers, procurement and supply management managers and manufacturers. When planning the introduction of new products, the following procurement and supply management-related factors should be considered.

- ☑ Is the product subject to patent or other intellectual property protection that would restrict access to generic formulations of the product in your country? Access to generic versions of ARV drugs is restricted in many middle-income countries. If this is the case, advice is available from WHO *(418)*.
- ☑ Is the product registered for use in your country? If not, consider obtaining a temporary waiver and in the meantime accelerate the official registration processes for future procurement. This information should be available from the national regulatory authority. Although the manufacturer is responsible to arrange registration, registering a drug in all countries can be a lengthy and expensive process.
- ☑ What is the forecasted demand for the product, including the anticipated pace of adoption? The pace of adoption is very difficult to forecast accurately, and ordering and delivery schedules must consider this unpredictability. More rapid adoption may lead to stock-outs if the procurement plan did not consider this, whereas a slower pace could lead to expiry of stocks if the procurement plan assumed faster adoption. Procurement and supply management managers need to monitor consumption closely and have risk mitigation strategies in place. If adoption is more rapid, suppliers should be asked to be prepared to respond to urgent orders. If adoption is slower, suppliers should be asked to deliver quantities gradually according to country requests until all the quantities ordered are consumed. Ordering in large volumes has the advantage of economies of scale, but suppliers should be flexible enough to send deliveries according to national demand to prevent expiry and wastage. Procurement and supply management managers are encouraged to work with HIV programme managers in formulating risk mitigation plans to account for the difficulty of accurate forecasting of demand and the pace of adoption.

- ☑ How will introducing the new product affect the use of existing medicines or diagnostics? Unless it is recommended that a product be stopped because of severe toxicity or other reasons, procurement and supply management managers should always plan to optimize use of existing stocks and orders before completely switching to new products to avoid wastage.
- ☑ How will purchasing the new product affect procurement budgets? Procurement and supply management managers may consult major global buyers and others to gauge the expected price so that quantities of existing and new products can be accommodated within the available budget. In some cases, lack of sufficient funds has delayed a full transition to new products that were more expensive or led to stock-outs of existing products.
- ☑ What is the shelf life of the product and how might this affect the procurement strategy and the in-country distribution of the product?
- ☑ Does the new product require any special handling or storage, such as temperature control? Consider adjusting the capacity and storage conditions of current facilities.
- ☑ What is the production status of the new product? What minimum order will the supplier accept, and what is the anticipated lead time from order placement to delivery? For products in lower demand, manufacturers may only be willing to commit to production once they are assured of commercially viable orders.
- ☑ If small volumes of new products are required, procurement and supply management managers should consider collaborating with neighbouring countries or global pooled procurement mechanisms to reach total order volumes that are viable for the manufacturers. This strategy may be particularly appropriate for second- and third-line formulations and for ARV drugs for children.
- ☑ Policy-makers and procurement and supply management managers may consult global buyers and other knowledgeable entities to gain market intelligence on new formulations while they develop strategies to introduce these new formulations through national procurement.

Points to consider for setting the remaining shelf life of medical products on delivery *(419)*

Decisions on remaining shelf life for medical products should be defined realistically, contextualized and adapted to each importer, following thorough risk assessment considering the criteria below. It should be defined and be based on relevant factors, including but not limited to the category and type of product; inventory level; manufacturing and transit lead time; local release lead time; storage condition; delivery chain; and resources in the recipient country or region.

Suppliers, purchasers and recipients should make agreements covering the relevant responsibilities of each party, including remaining shelf life or expiry date.

Products should be transported, received, stored and distributed in accordance with WHO good storage and distribution practices *(420)*. Special attention should be given to products sensitive to temperature, light and moisture.

Products supplied by the manufacturer or supplier should comply with the policy of the national government and the recommendations on remaining shelf life prescribed here.

Products should be appropriately labelled. The label should include the expiry, retest or install by date, as appropriate.

The products received should be scrutinized in an attempt to identify possible substandard and falsified products. For example, ensure that the expiry date is not falsified *(421)*.

If different periods for remaining shelf life have been defined for products, recipients should ensure that the products meet the remaining shelf-life requirement for the intended destination, such as a central warehouse, regional warehouse, testing site or user point.

National authorization for importation, if required, should be obtained based on the available information, including the expiry date of the product, to enable the remaining shelf life to be calculated and to assist in expediting approval.

When justified, suppliers, recipients and national authorities may negotiate deviations from the policy for remaining shelf life. If the remaining shelf life is shorter than stipulated in the policy, ensure that the stock will be consumed before expiry and that the medical product reaches end-users with adequate remaining shelf life to permit confidence on the time to consume it before expiry.

Risk should be assessed with the following considerations to ensure that the parameters listed above are met:

- assessment of need;
- type of product: different implications in terms of patient safety with respect to pharmaceutical products, vaccines, medical devices and in vitro diagnostic products;
- expiry date: with this, the remaining shelf life at delivery time can be estimated;
- compliance with WHO guidelines on good storage and distribution practices *(418)*;
- delivery time to storage facility;
- storage conditions;
- stock rotation;
- delivery time from storage to end-user;
- frequency of stock replenishment – order frequency (based on consumption): recipients and end-users should regularly verify that medical products in stock are rotated or used within their remaining shelf life and adjust the quantities ordered to ensure that the medical products will be used within their remaining shelf life;
- assessment of the real needs, to ensure that the medical products can be used within their shelf life;
- emergencies: during an emergency situation, the policy on remaining shelf life should be well balanced to ensure that life-saving medical products will be received on time and that the needs will be covered if there is increased demand;
- logistic set-up: the location of the premises, the number of means and types of transport and the number of vehicles and their adaptability will affect the speed of delivery and therefore the confidence that products will be used before their expiry date; and
- activity specificities: similarly, whether the medical products will be used by the national programme or are managed directly by the importer outside of a national programme will make a difference in terms of speed of delivery to the end-user. The point of delivery – national warehouses or importer or end-user facilities – will also affect the speed of delivery.

Useful procurement and supply management resources

This document does not cover all technical issues related to supply chain management. The Procurement & Supply Management Toolbox *(422)* contains procurement and supply management tools that can be searched by technical area and by publishing organization.

7.14 Laboratory and diagnostic services

Overview

Implementing the recommendations in these guidelines will require increased access to laboratory and diagnostic services.

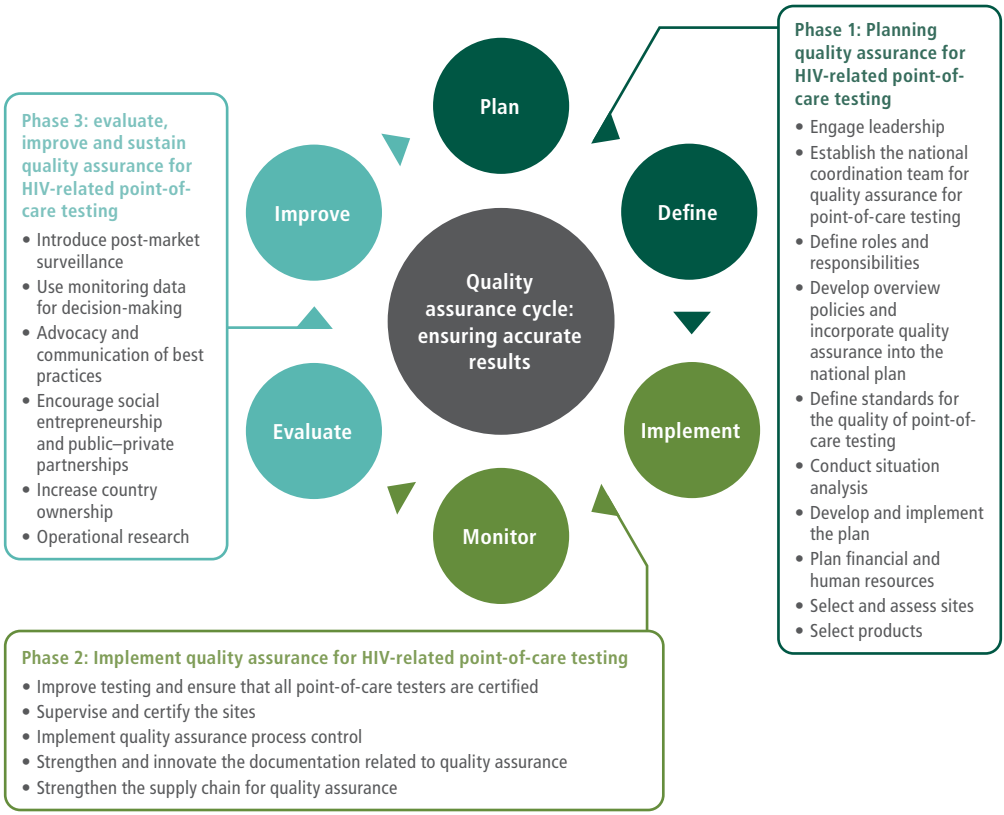
To ensure that diagnostic services are accurate and reliable, relevant quality assurance systems need to be developed and strengthened. Within a country, a multiplicity of diagnostic settings may exist, such as laboratories, maternal and child health clinics, HIV testing and counselling sites and community-based testing. A multipronged and networked approach to selecting diagnostics and laboratory systems should therefore be planned and adopted. Because many new diagnostic tests and point-of-care systems are entering the market, the use of only high-quality diagnostics and equipment needs to be ensured. Strategic planning for proper placement and harmonization of testing platforms should be carried out to ensure appropriate use and cost–effectiveness.

Effective laboratory and diagnostic services require sound leadership and governance to enable the following activities *(423)*:

- strengthening and expanding laboratory and diagnostic services;
- supporting a dedicated specimen referral system;
- increasing access to HIV diagnostics, including infant diagnosis, CD4 and viral load testing;
- supporting the expansion of diagnostic services to include testing at the point of care;
- training and certifying health-care workers who perform testing; and
- ensuring high-quality diagnostics and plans for implementation, including quality assurance.

WHO and the United States Centers for Disease Control and Prevention have developed a guidance handbook on quality assurance approaches for point-of-care tests and laboratories in low- and middle- income countries (Fig. 7.10) *(424)*.

Fig. 7.10 Three phases of diagnostic quality assurance



Strengthening and expanding laboratory and diagnostic services

The following areas are important to strengthen the network of laboratory and diagnostic services for implementing the recommendations in these guidelines:

- national laboratory strategic plans and policies;
- reviewing available diagnostics for their performance and operational characteristics to select optimal products before introduction;
- carrying out strategic planning and diagnostic network optimization for properly placing and harmonizing testing platforms to ensure appropriate use and cost–effectiveness;
- expanding current diagnostic networks to support and monitor expanded access as well as decentralization and integration of testing and diagnostic services;
- allocating appropriate resources to ensure the availability of diagnostic tests, including human and financial resources, and
- guidance on operations and service delivery.

Supporting a dedicated specimen referral system

When point-of-care testing is unavailable, laboratory referral systems and procedures for collecting and processing specimens need to be strengthened to increase access to viral load testing and other testing needs. Providing for and strengthening an integrated, efficient, safe and cost-effective specimen referral system requires reliable specimen transport with adequate conditions for whole blood, plasma, dried blood spot specimens and other potential alternative specimen types that rapidly and dependably reports test results back to the referring site with linkage to care. Integrating specimen referral systems across diseases may be a beneficial consideration to leverage those already in use and create system efficiency across programmes.

Increasing access to HIV diagnostics

These guidelines recommend the use of several HIV diagnostics including infant diagnosis, CD4 and viral load testing. This will require ongoing strengthening of existing diagnostic services and phased expansion of monitoring services in peripheral facilities. It may involve:

- strengthening, leveraging and integrating diagnostics within existing networks;
- ensuring that health-care facilities and laboratories have adequate infrastructure, human resources, technical expertise, service and maintenance programmes, quality assurance mechanisms including supervision and monitoring of supply chain management and quality improvement programmes; and
- ensuring the optimization of high-volume centralized laboratory testing and testing at the point of care across all testing needs, giving priority to the people most at risk for morbidity and mortality.

Table 7.5 Tiered laboratory network at various levels of the health-care delivery system

Health care delivery level	Laboratory service	Quality assurance actions	Human resources
National reference laboratory	• Enzyme immunoassays for diagnosis • Higher-throughput CD4 • HIV molecular technologies including HIV viral load testing and quantitative and qualitative infant diagnosis • HIV resistance testing	• Performing quality assurance activities for services provided • Validating point-of-care testing • Training and certification • Coordinating quality assurance • Proficiency testing • Confirmatory testing • Collecting and analysing data • Corrective action	• Senior laboratory specialists • Senior laboratory supervisors • Trainers • Senior technicians

Health care delivery level	Laboratory service	Quality assurance actions	Human resources
Regional or provincial reference laboratory	• Enzyme immunoassays for diagnosis • Higher-throughput CD4 • HIV molecular technologies including HIV viral load testing and quantitative and qualitative infant diagnosis	• Rapid diagnostic tests, point-of-care tests for CD4, infant diagnosis and viral load • Performing quality assurance activities for services provided • Coordinating regional training and quality assurance • Collecting and analysing data • Corrective action	• Laboratory supervisors • Trainers • Senior technicians
District-level laboratory	• Enzyme immunoassays for diagnosis • Lower-throughput CD4 • Point-of-care infant diagnosis, viral load and CD4 • HIV rapid diagnostic tests, chemistry, haematology and microbiology • Collecting whole-blood and/or DBS specimens	• Performing quality assurance activities for services provided • Supervising sites • Corrective action	• Laboratory technicians • Laboratory assistants
Primary care setting	• HIV rapid diagnostic tests • Point-of-care infant diagnosis, viral load and CD4 • Collecting whole-blood and/or DBS specimens	• Performing quality assurance activities for services provided	• First-level trained health-care workers such as nurses and clinical officers • Trained professional and non-professional staff
Community-based and community outreach	• HIV rapid diagnostic tests • Collecting finger-prick and/or DBS specimens for testing	• Performing quality assurance activities for services provided	• Community health-care workers

Source: adapted from: *WHO expert meeting report on short, medium, longer term product development priorities for HIV-related diagnostics, 6–7 June 2012, Geneva, Switzerland (424)* and *Improving the quality of HIV-related point-of-care testing: ensuring the reliability and accuracy of test results (423)*

7.15 Laboratory connectivity

Recommendation (2016)

Electronic communication can be considered to transfer test results and reduce delays in acting on the results of infant diagnosis and other essential laboratory tests *(conditional recommendation, low-certainty evidence)*.

Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – second edition (3)*

The decentralization of HIV care to lower levels of the health system has enabled expanded access to treatment and improved outcomes. One challenge to delivering care at peripheral facilities has been to ensure the rapid and reliable turnaround of laboratory results. Lack of efficient sample transport systems can result in delays in or losses of results, which in turn can delay clinical decision-making.

Although this can be partly overcome by using technologies such as point-of-care devices or rapid tests that provide results on the same day as specimen collection, if these are unavailable, alternative approaches are needed to minimize delays in turnaround time of essential laboratory results, especially for infant diagnosis. SMS/GSM/GPRS printers represent a potential solution, whereby laboratories can transmit SMS/GSM/GPRS-based messages to the clinic site in real time via standard telecommunication networks. Several countries have well-established programmes using SMS/GSM/GPRS printers, including Kenya, Mozambique, Rwanda, South Africa, Zambia and Zimbabwe. Several other countries are in the implementation and pilot phases of SMS/GSM/GPRS printer use.

Rationale and supporting evidence

A systematic review was conducted focusing on the potential for electronic systems for delivering results to reduce the turnaround time of early infant HIV diagnostic test results *(425)*. Mortality among infants living with HIV is highest during the first three months, and early HIV diagnosis and early ART can significantly reduce this risk *(426)*. Turnaround times using traditional paper-based systems can extend to about two months, leading to loss to follow-up of mothers and their infants and increased infant mortality if treatment is delayed.

The review identified 11 studies, all from Africa, and found that the use of SMS/GPRS printers reduced the average turnaround time by 17 days (from 68 to 51 days), with several studies reporting a turnaround time of less than 20 days. The evidence was rated as low quality because of the absence of randomized study designs and lack of data on clinical impact. Because similar efficiency could possibly be obtained for other laboratory results, electronic systems for delivering results could be used for other tests such as CD4 count testing, viral load testing and other non-HIV-related testing.

Cost

No formal cost–effectiveness analysis was conducted. However, the Guideline Development Group judged that the cost of the intervention would be offset by the substantial health benefits related to earlier identification of HIV-positive infants.

Equity

The technology aims to improve access to results in rural settings and, as such, the Guideline Development Group judged that it would improve equity.

Feasibility

Feasibility has already been demonstrated by applying SMS/GMS/GPRS printers in a variety of settings.

Implementation considerations

Adequate cellular phone network coverage, maintenance, troubleshooting and systems for ensuring a supply of sufficient credit and printer consumables are all key to ensuring coverage and uninterrupted service.

Implementation should consider the need to ensure data security and patient confidentiality.

Research gaps

Further studies should assess the clinical impact of SMS/GSM/GPRS printers on loss to follow-up, mortality and morbidity. It would be useful to assess the utility and impact of using SMS/GSM/GPRS printers and results return technologies for returning a range of laboratory results.

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8. MONITORING ART PROGRAMME FUNCTIONING

8.1 Introduction

Monitoring and evaluation of HIV care and treatment helps programme managers to assess the effectiveness and uptake of interventions and establishes links between services along the cascade starting with HIV diagnostic testing and subsequently linking to treatment and care for HIV and associated conditions. As countries adopt and implement these guidelines, monitoring and evaluation frameworks and systems will need to collect and analyse information to support the implementation and uptake of new recommendations. Robust and actionable information measuring ART programme functioning is essential to identify and characterize the gaps and bottlenecks in programme performance and to adequately respond and address them. Patient monitoring systems that link and communicate with one another are needed to track people receiving care as they move between clinics and districts over time and to ensure retention in care. As programmes mature, monitoring of individual- and national-level outcomes, including new HIV diagnoses, ART coverage, viral suppression, mortality, survival, toxicity and adverse reactions and the emergence and transmission of drug-resistant HIV becomes increasingly essential to assess the quality and impact of programmes and to further contribute to their optimization over time.

Data on HIV testing and treatment outcomes can be collected in many ways, including routinely reported data from everyone across all facilities (census) or from sentinel sites; district health information systems; population-based surveys; case surveillance data; observations from cohorts of people living with HIV; and periodic evaluation. Programme input and processes can also be monitored through facility surveys or updated lists of service availability; documenting the availability and training of human resources; and monitoring the availability of HIV medicines and diagnostics at various levels of the health system.

In considering how best to collect critical patient and programme data, efforts should be made to review current monitoring systems and to link, to the extent possible, the monitoring of TB, ART and conditions related to advanced HIV disease, including the addition of quality-of-care indicators relevant to the emergence and transmission of drug-resistant HIV (early warning indicators of HIV drug resistance) into routine health information systems. Special surveys can be considered when data collected through routine monitoring systems are insufficient to answer specific questions or if the routine monitoring system does not yield reliable information.

Involving civil society in monitoring and evaluation activities is also critical to better understand successes and failures, especially in assessing the determinants, perceptions, values and experiences of people living with HIV, key populations and the broader community in accessing and using services.

8.2 Selection of key indicators to improve service delivery and assess impact

The 2020 WHO consolidated HIV strategic information guidelines *(1)* provide comprehensive guidance on monitoring national and global health sector responses to HIV, including the use of ARV drugs for treatment and prevention. These guidelines recommend a set of indicators of high utility for certain countries differentiated by specific epidemiological characteristics – for example, a high burden of comorbidities of HIV and TB or hepatitis B and C.

The guidelines propose 40 national priority indicators, including 15 national core indicators plus an additional 25 indicators that are feasible to collect and provide programme managers the information needed to improve services (Table 8.1, Fig. 8.1). The top 40 indicators are those most relevant to effective programme management in accordance with national strategy and clinical guidelines anchored in WHO technical guidelines. Fifteen national core indicators are recommended as essential for tracking progress against national targets. The national core indicators gauge critical aspects of coverage and quality and highlight international strategic, programmatic and clinical imperatives. These 15 indicators are widely applicable across country contexts and are recommended for all countries. An additional 25 indicators are suggested to provide programme managers with additional information and evidence needed to improve services. Combined, these top 40 indicators are those most relevant to effective programme management in accordance with national strategies and clinical guidelines anchored in WHO technical guidelines.

Countries are encouraged to consider including the recommended national core and priority indicators in their national monitoring and evaluation framework and health information systems. Standardized definitions and references are presented in the guidelines *(1)* to ensure comparability with other global HIV monitoring and evaluation frameworks, including UNAIDS Global AIDS Monitoring, the Global Fund Modular Framework and PEPFAR Monitoring, Evaluation and Reporting indicators. Such data standardization and alignment are essential in facilitating both the development of robust, interoperable health information systems and data use models at the country level and in ensuring high-quality and comparable data for global monitoring.

The indicators recommended for the national core span the breadth of the cascade, reflect the critical aspects of coverage and quality and highlight international strategic, programmatic and clinical imperatives tied to outcomes and impact. They form the essential basis of routine data reviews to improve programmes at the national, district and facility levels. National HIV programme indicators of particular importance to the implementation of these guidelines include those that relate to:

- reducing the number of people at substantial risk acquiring HIV;
- 95% of people living with HIV knowing their status and being linked to treatment;
- 95% of people living with HIV receiving ART and, of those, 95% achieving viral suppression;
- reducing mortality (TB);
- reducing the number of children acquiring HIV; and
- reducing comorbidity and mortality (sexually-transmitted infections).

Detailed indicator tables for each programme area along the testing, treatment and care cascade are available in Part 3 of the 2020 WHO consolidated HIV strategic information guidelines *(1)* and provide instructions for data collection and methods of measurement for each of the 40 indicators.

Table 8.1 Recommended national core and national priority indicators[a] *(1)*

Strategic objective (reference number prefix)	Programme domain	Top 15 (national core)	Top 40 (national priority)
Reduce the number of people at substantial risk acquiring HIV (PR)	Condoms	PR.1 Condom use (key populations and the general population)[b]	PR.2 Condoms distributed
	PrEP	PR.3 PrEP uptake	PR.4 PrEP continuation (at 3 months) PR.5 Currently on PrEP
	Other prevention	KP.1 Coverage of HIV prevention (key populations)[b] KP.2 Needles and syringes distributed	KP.3 Coverage of opioid substitution therapy KP.4 Safe injecting practices (people who inject drugs)[b] GW.1 Adolescent girls and young women HIV and sexual and reproductive health integration
95% of people living with HIV know their HIV status and are linked to treatment (TL)	HIV testing services	TL.1 People living with HIV who know their HIV status (first 95) TL.2 HIV testing volume and positivity TL.3 Linkage to ART	TL.4 HIV testing services index testing and partner notification TL.5 HIV self-testing distribution TL.6 Know their status (key populations)
95% of people living with HIV identified as receiving ART and 95% viral suppression for those receiving ART (AV)	ART and viral load	AV.1 People living with HIV receiving ART AV.2 Total attrition from ART AV.3 People living with HIV who have suppressed viral load	AV.4 New ART patients AV.5 Late ART Initiation AV.6 Viral load testing coverage AV.7 Early viral load testing (at 6 months) AV.8 Appropriate second viral load test AV.9 ARV toxicity prevalence
Reduce mortality (TB)	TB and HIV	TB.1 TB preventive treatment initiation TB.2 TB preventive treatment completion	TB.3 TB diagnostic testing type TB.4 People living with HIV with active TB disease
Reduce the number of children acquiring HIV (VT)	Vertical transmission	VT.1 Viral suppression at labour and delivery VT.2 Early infant diagnosis coverage	VT.3 Infant ARV drug prophylaxis coverage VT.4 ART coverage among pregnant women VT.5 ART coverage among breastfeeding mothers VT.6 Final outcome of preventing mother-to-child transmission

Strategic objective (reference number prefix)	Programme domain	Top 15 (national core)	Top 40 (national priority)
Reduce comorbidity and mortality (ST)	Sexually transmitted infections		ST.1 Syphilis screening coverage (in antenatal care) ST.2 Syphilis treatment coverage (in antenatal care) ST.3 Cervical cancer screening among women living with HIV

[a] Standard disaggregation by age, sex and key population status is recommended for these priority indicators to ensure that the way HIV services are delivered meets the needs of different subpopulations.

[b] Survey-based indicator.

8.3 Data collection and disaggregation

A core component of cascade analysis – of both aggregate and individual-level data – is the disaggregation of indicators by specific geographical and sociodemographic subpopulations or important patient subgroups. This type of analysis enables managers to address issues of both programme performance and equity in terms of access and service quality. In the interest of improving programme performance, the fastest way to achieve overall programme targets lies in identifying and addressing the barriers for the most underserved groups. Disaggregated analysis enables these subpopulations to be identified, which can be described either by geography (for example, region or province, district or county or facility) age, sex, key population and other important characteristics that require differentiated management or services (for example, pregnant women and people with both TB and HIV). Indicators include disaggregation by priority population or population-specific indicators that reflect the relative contribution of these groups to the epidemic and monitoring the performance of programme services for these groups. To achieve programme effectiveness and equity, programmes must commit to services reaching all people in need and to leaving no one behind. Routine assessment of equity in service delivery and quality across groups is fundamental to measuring and tracking these commitments.

All data collected must be strictly treated as confidential, especially for members of key populations, who face significant stigma and discrimination. All data should be stored securely, and the staff collecting and storing data should be properly trained to maintain patient (or client) confidentiality.

8.4 Strengthening data systems

As countries plan investment in their data systems, considering the strengths and limitations of each data source is important for the interpretation and intended use of the information generated. To be sustainable, the strategic information system of the health sector response to HIV must align with the broader health information system as part of an integrated architecture. Guidance for national health information system standards, guidelines and tools is available to support the development of appropriate health information system and digital health policies, guidelines, strategic plans and road maps, including maturity models for system interoperability.

Most countries manage a complex system of individual patient-level data and/or aggregated data. Patient information systems typically interface (directly, via interoperability, or indirectly, via manual data transfer) with laboratory and pharmacy information systems to efficiently capture essential information for use in routine cascade analysis and in data validation and quality assessment. This variation and complexity in data systems result from differences in local infrastructure capacity, digital health leadership and planning and the resources invested in building and maintaining systems. Making disparate ways of reporting coherent is critical to being able to comprehensively assess programme performance through routine cascade data reviews.

Although most routine health information systems are based at health facilities, effectively monitoring and managing programmes also require data from community-based services. Thus, data systems increasingly must be able to capture and integrate data on the delivery of community-based services, delivered via mobile or satellite clinics and often by peer or outreach workers. Community-based services are especially important for members of higher-risk populations who may not otherwise seek services at health facilities. Consequently, large gaps in understanding the coverage and quality of service delivery to these populations will exist unless routine systems incorporate data from community-based services.

The national monitoring and evaluation plan or framework for HIV should incorporate data from multiple sources with uses at different management levels. The major data sources are shown in Fig. 8.1. Most core data elements in primary data collection tools have multiple uses, such as for aspects of patient care and monitoring, programme management and programme monitoring. Indicators should be reviewed regularly to ensure that all data collected are clearly useful.

Fig. 8.1 Overview of five key sources of strategic information on HIV in the health sector

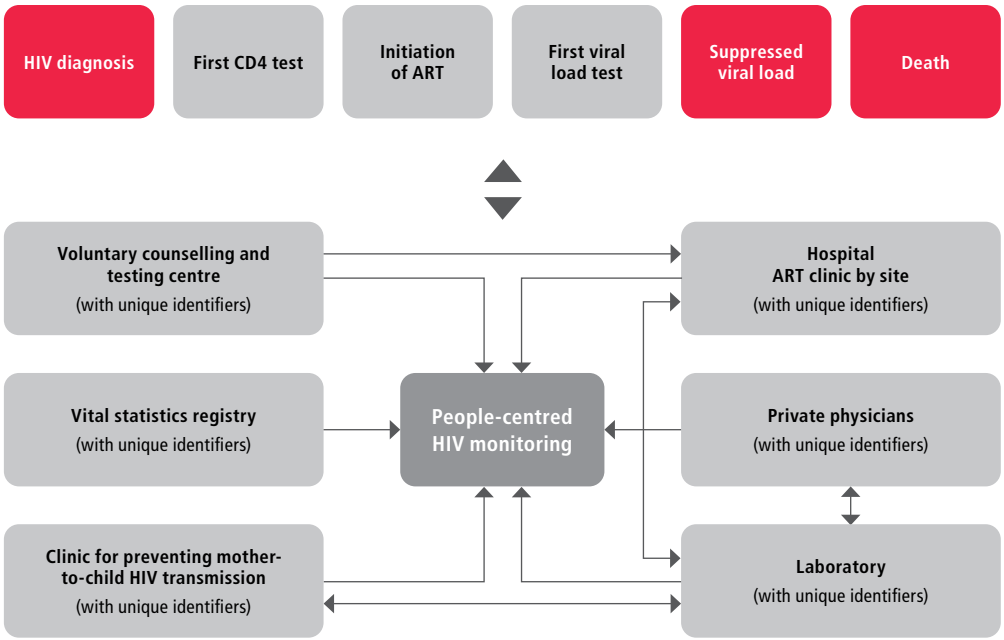
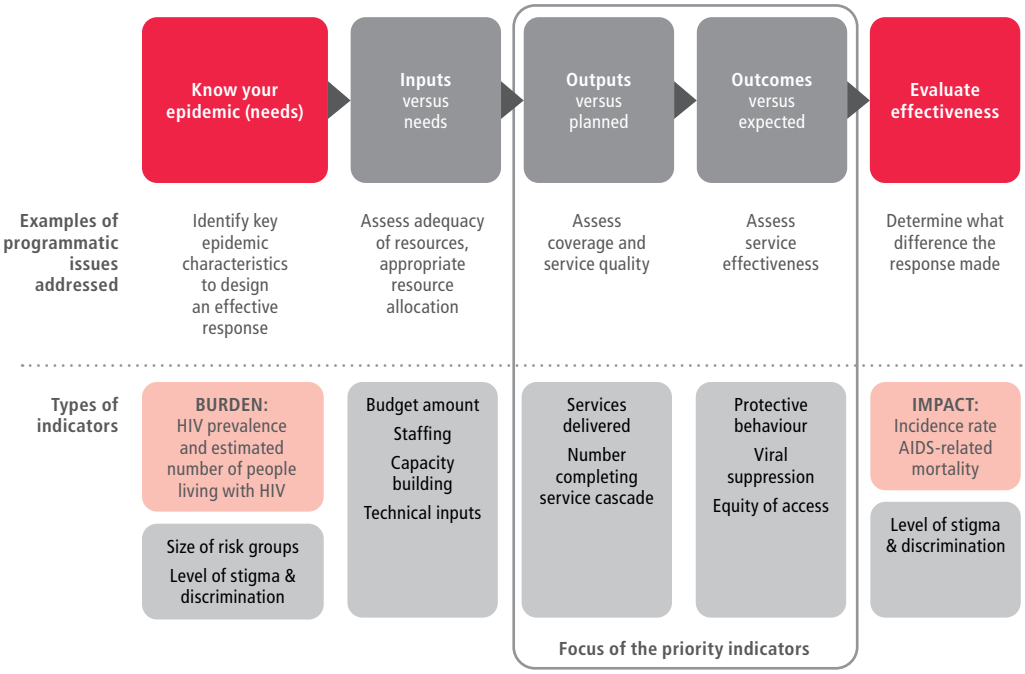


Fig. 8.2 HIV results chain



8.5 Evaluation, including impact and programme performance

The health sector response to HIV can be monitored through a coherent results chain of selected key input, output, outcomes and impact (Fig. 8.2). The indicators recommended in the WHO 2020 strategic information guidelines span the full results chain but most strongly emphasize tracking the output of coverage and quality and key programmatic and clinical outcomes: that is, those most useful for routine programme monitoring and management *(1)*.

Measuring the HIV cascade of services – improving links from testing to prevention and treatment

As described in the WHO *Cascade data use manual (2)*, the critical outputs and outcomes of the health sector response to the HIV epidemic can be visualized through a cascade of services anchored by the 95–95–95 targets for 2030. Cascade analysis helps to identify trends, progress, gaps and bottlenecks in service delivery and to develop solutions and improvements. In a cascade, the measures of service coverage are represented as sequential bars for each service area. Further, the cascade format highlights gaps between bars to indicate the quality of patient follow-up and coordination between service areas and, ultimately, service access.

Strengthening the analysis and use of data at each stage of the cascade is key: from primary prevention among those at substantial risk of HIV infection to viral suppression for those on treatment. There are multiple formats for displaying cascades to gain different perspectives on the epidemic and response, for example, to assess gender equity and age-specific differences in coverage, to ensure the quality of services for specific subgroups, to review current or long-term performance or to compare population-based versus programme-based performance.

Regular programme reviews should assess each stage of the testing, prevention and treatment cascade to identify and measure progress, gaps and relations to trends in incidence and mortality.

8.6 Monitoring ARV drug toxicity

In June 2020, WHO published a technical update that outlined the key recommended indicators and approaches and tools for monitoring ARV drug toxicity *(3)*.

The transition to DTG as the preferred first-line ART is an opportunity to optimize and standardize HIV treatment, but it also poses certain risks, such as the potential for new types of drug-related toxicity and suboptimal treatment outcomes. Recent data suggest a potential risk of weight gain associated with newer ARV drugs (notably DTG and TAF) and highlight the need for active toxicity monitoring in countries as they scale up or introduce these drugs *(4)*. The signal of neural tube defect potentially associated with DTG in May 2018 reinforced the importance of robust data and surveillance systems to evaluate the safety of new ARV drugs for pregnant women and their unborn children in low- and middle-income countries *(5)*. WHO recommends that countries consider a combination of approaches to monitor ARV drug toxicity and promote patient safety, including surveillance of maternal, fetal and neonatal safety of ARV drugs used in pregnancy and active and routine toxicity monitoring in all populations, including adults, adolescents and children *(6–8)*.

8.6.1 Routine monitoring for ARV toxicity

The 2020 HIV consolidated strategic information guidelines *(1)* recommend the percentage of people receiving ART with treatment-limiting toxicity as the priority indicator for monitoring ARV toxicity. Treatment-limiting toxicity is defined as a life-threatening illness, death, hospitalization, disability or a serious adverse drug reaction that results in drug discontinuation or substitution *(1)*.

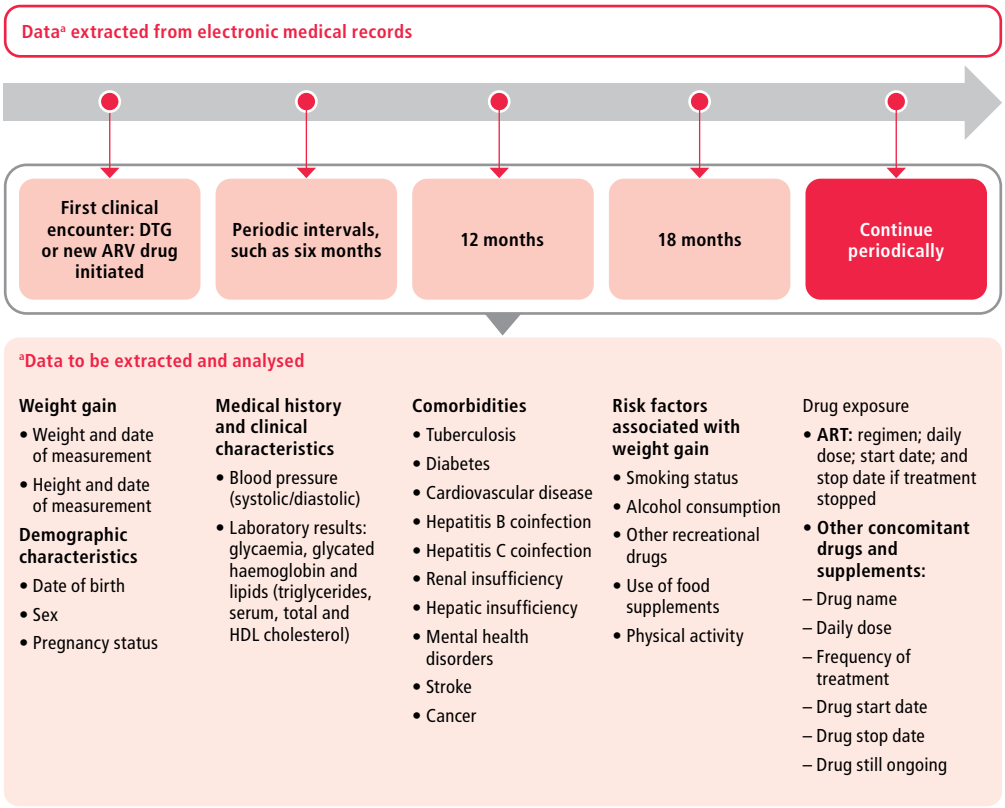
This indicator measures the prevalence of serious ARV drug toxicity among people receiving ART. Routine monitoring integrated into routine HIV patient monitoring systems will provide data on the clinical significance of serious toxicity and how this affects patient outcomes and attrition. Information on the prevalence of toxicity will inform national guidelines and efforts to prevent and limit ARV drug toxicity.

8.6.2 Longitudinal monitoring recommended to address emerging concerns and risk factors related to ARV drug toxicity

In 2017, WHO recommended linking the active toxicity monitoring of new ARV drugs to existing pharmacovigilance systems when possible to provide a robust complementary approach to routine monitoring *(8,9)*. Actively monitoring adverse drug reactions remains critical and should continue. To this end, tools developed by WHO are available to support country implementation *(9)* (Fig. 8.3).

With recent results from clinical trials and cohort studies showing a potential risk of excessive weight gain with the use of DTG with and without TAF *(4)*, WHO encourages countries to implement longitudinal monitoring of people living with HIV over time to assess changes in body weight or body mass index, screening of risk factors and assessment of the impact on metabolic comorbidities and cardiovascular disease and on maternal and pregnancy outcomes. Longitudinal monitoring complements adverse drug reaction reporting with the use of clinical data from patient records to detect temporal patterns in adverse drug reactions or risk factors that develop among people living with HIV over time *(3)*.

Fig. 8.3 Longitudinal monitoring of adverse drug reactions and clinical characteristics among people receiving ARV drugs



In addition, the 2020 guidelines *(1)* recommend collecting information on the programmatic reasons for switching ART regimens or treatment interruption, defined as the percentage of people receiving ART who switch or stop their ARV drug regimen *(9)*. Disaggregation by age (<15, 15–19, 20–24, 25–49 and ≥50 years), gender (male, female or transgender), key population (men who have sex with men, sex workers, people who inject drugs, people in prisons and other closed settings and transgender people) and geographical and other administrative areas of importance provides additional information on populations at higher risk for toxicity because of environmental and behavioural factors.

The 2020 guidelines *(1)* also recommend a new indicator for monitoring PrEP-related ARV drug toxicity: the proportion of people who received oral PrEP who have discontinued or interrupted PrEP during the reporting period because of serious toxicity related to ARV drugs. The monitoring and evaluation module (module 5) of the WHO implementation tool for PrEP outlines the recommended approaches for monitoring the toxicity of PrEP along with generic PrEP user cards and tools for monitoring adverse drug reactions *(10)*.

8.6.3 New indicators for routine monitoring of adverse pregnancy outcomes related to exposure to ARV drugs

Four indicators are now recommended to monitor adverse pregnancy outcomes related to exposure to ARV drugs *(1)*:

- the proportion of low-birth-weight (<2.5 kg) deliveries among women living with HIV;
- the proportion of stillbirths or miscarriages among women living with HIV;
- the proportion of preterm deliveries (<37 weeks of gestation) among women living with HIV; and
- the proportion of women living with HIV with conception and first-trimester (<14 weeks of gestation) ART exposure who have an infant with a major external congenital anomaly.

A higher than expected rate of adverse pregnancy outcomes based on these indicators suggests a need for more formal assessment, such as through birth defect surveillance or pregnancy registries *(8)*.

8.6.4 Global surveillance of the safety of ARV drugs for adults, children and adolescents and in pregnancy

Building on the toxicity monitoring efforts at the country level, WHO has developed a central database for the surveillance of the safety of new ARV drugs for adults, adolescents and children. The goals of the database are to facilitate the pooling of safety data collected by countries and partners, to increase sample sizes, to generate more rapid evidence on the safety profile of new ARV drugs and to detect toxicity signals.

WHO has established a similar collaborative initiative to generate data on the safety of drugs in pregnancy through a central registry for epidemiological surveillance of drug safety in pregnancy. Further information, including tools and training materials, is available at: https://www.who.int/tdr/research/tb_hiv/drug-safety-pregnancy/en.

8.7 HIV drug resistance

As ART is scaled up, the emergence of significant population-level HIV drug resistance to NNRTIs and NRTIs has become a global concern. HIV drug resistance is associated with poor clinical outcomes and reduced effectiveness of ARV drugs, threating the effectiveness of ART and sustained reductions in HIV-related morbidity and mortality.

The 2019 WHO global report on HIV drug resistance *(11)* documented a high prevalence of pretreatment HIV drug resistance to EFV and/or NVP among adults initiating first-line ART, exceeding 10% in several low- and middle-income countries in all regions of the world. The overall prevalence of pretreatment HIV drug resistance to EFV and/or NVP was more than twice as high ($p \leq 0.0001$) among people starting first-line ART reporting previous ARV drug exposure (21%, 95% CI 15–29%) versus people without previous ARV drug exposure (8%, 95% CI 6–10%). Moreover, the prevalence of EFV and/or NVP resistance was twice as high among women (12%, 95% CI 9–15%) as among men (8%, 95% CI 6–10%).

The clinical impact of HIV drug resistance is significant. A recent systematic review and meta-analysis concluded that people initiating NNRTI-based ART with pretreatment HIV drug

resistance are about three times more likely to experience viral non-suppression (OR 3.07, 95% CI 2.40–3.94), to acquire new resistance mutations (OR 2.45; 95% CI 1.70–3.52) and discontinue or switch ART (OR 3.25; 95% CIW 1.86–5.67) as those without pretreatment HIV drug resistance *(12)*. These data informed WHO's guidelines on the public health response to pretreatment HIV drug resistance *(8)*, which recommend that countries move away from NNRTI-based first-line ART when national surveys show levels of pretreatment HIV drug resistance at or above >10%. Globally, increasing high levels of pretreatment HIV drug resistance to NNRTI among adults initiating ART emphasize the need to fast-track the transition to DTG-based first-line ART regimens.

The emergence of resistance among children is also concerning. The 2019 WHO HIV drug resistance report *(11)* showed that more than half of the treatment-naive infants newly diagnosed with HIV in several sub-Saharan African countries had HIV that was resistant to NNRTIs *(11)*. Levels of resistance to NRTIs were also high, ranging from 2% to 26%. The high levels of pretreatment HIV drug resistance among children ≤18 months old underscore the need to accelerate access to child-friendly non-NNRTI-based ART formulations and to rationally sequence ARV drug regimens.

The 2019 WHO global report also documented a high prevalence of acquired drug resistance among people receiving NNRTI-based ART with unsuppressed viral load from several low- and middle-income countries. The prevalence of NNRTI resistance ranged from 50% to 97%, and resistance to the most commonly used NRTIs ranged from 21% to 91% *(11)*. The high prevalence of HIV drug resistance among people with unsuppressed viral load receiving NNRTI-based first-line ART demonstrates the degree to which NNRTI-based regimens are compromised for people failing treatment, indicating the need for rapid switch to second-line ART when viral load >1000 copies/mL is detected. The high levels of resistance to tenofovir and dual resistance to tenofovir and 3TC or FTC among individuals receiving ART with unsuppressed viral load support the need for careful considerations around the selection of NRTI backbone when transitioning from TLE to TLD.

Resistance to DTG is currently generally low, and efforts to prevent the emergence of resistance to this drug should be given priority. WHO recommends that programmes monitor levels of resistance to integrase inhibitors in populations starting ART and among people for whom ART has failed. In addition, as countries scale up PrEP, monitoring for resistance at the population level becomes increasingly important, and WHO developed guidance to support countries in this effort *(13)*. The integration of HIV drug resistance prevention, monitoring and response is an essential component of successful ARV drug stewardship, and routine, standardized surveys of HIV drug resistance should be integrated into every national HIV plan (Box 8.1).

Box 8.1 WHO recommendations to countries to prevent, monitor and respond to HIV drug resistance

WHO recommends that countries include the following priority activities in their national HIV strategic plan for the purpose of planning and budgeting and for inclusion in their funding requests:

- developing a national action plan on HIV drug resistance, which should be integrated into the national HIV strategic plan and should be in accordance with the five strategic objectives of the global action plan on HIV drug resistance *(14)*;
- annually monitor quality-of-care indicators (early warning indicators) of HIV drug resistance with accompanied appropriately locally tailored response to gaps in service delivery identified by this process;
- periodic surveys of acquired HIV drug resistance in populations receiving ART (adults and children);
- periodic surveys of pretreatment HIV drug resistance among infants newly diagnosed with HIV and younger than 18 months of age;
- periodic surveys of pretreatment HIV drug resistance among adults initiating (or reinitiating) ART; and
- periodic surveys of drug resistance among people testing HIV positive and exposed to PrEP.

8.7.1 National action plans on HIV drug resistance

Increasing levels of resistance to ARV drugs could undermine the success of the scale-up of ART, and the broader national HIV response, if not addressed in a timely manner. Minimizing the emergence and transmission of drug-resistant HIV is a key component of the national HIV response. WHO recommends that HIV treatment scale-up be accompanied by measures to monitor and improve the quality of ART delivery and surveillance of HIV drug resistance.

WHO has coordinated the development of a global action plan for HIV drug resistance that includes five strategic objectives: (1) implement high-impact interventions to prevent and respond to the emergence of HIV drug resistance, (2) obtain quality data on HIV drug resistance from periodic surveys while expanding routine viral load and HIV drug resistance testing; (3) encourage relevant and innovative research that will have the greatest public health impact in minimizing HIV drug resistance; (4) support and expand the use of viral load testing and build capacity to monitor HIV drug resistance; and (5) ensure that country ownership, coordinated action, awareness, advocacy and sustainable funding are in place to support action on HIV drug resistance (Fig. 8.4) *(14)*. WHO regions have adapted the plan into regional action plans on HIV drug resistance *(15)*.

WHO recommends that countries develop a five-year national action plan on HIV drug resistance to endorse country ownership, periodic population-level HIV drug resistance assessments, leveraging of enablers and timely dissemination and use of all available HIV drug resistance information (Fig. 8.5). Activities within the national plan should be aligned with WHO global and regional action plan objectives and targets and integrated into the national HIV strategic plan.

Fig. 8.4 Strategic objectives of the national action plan on HIV drug resistance

Strategic objective 1: Prevention and response
Implement high-impact interventions to prevent and respond to the emergence of HIV drug resistance.

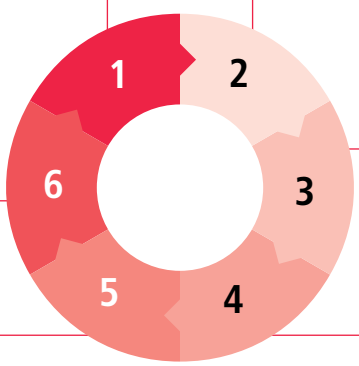
Strategic objective 2: Monitoring and surveillance
Obtain quality data on HIV drug resistance from periodic surveys while expanding routine viral load and HIV drug resistance testing.

Strategic objective 3: Research and innovation
Encourage relevant and innovative research that will have the greatest public health impact in minimizing HIV drug resistance; fill existing knowledge gaps on the risk of HIVDR for newer ARV drugs and the impact of service delivery interventions to increase viral load suppression and contain HIVDR.

Strategic objective 4: Laboratory capacity
Support and expand use of viral load testing and build capacity to monitor HIV drug resistance in low- and middle-income countries.

Strategic objective 5: Governance and enabling mechanisms
Ensure that country ownership, coordinated action, awareness, advocacy and sustainable funding are in place to support action on HIV drug resistance.

Fig. 8.5 Guiding principles of the national action plan on HIV drug resistance



Country ownership
- HIV drug resistance activities led by a national HIV drug resistance working group
- Integrating the national action plan on HIV drug resistance into the national strategic HIV plan
- Integrating HIV drug resistance activities into routine monitoring and evaluation systems

Timely dissemination of information

Use of all available information to minimize the emergence and transmission of drug-resistant HIV and inform optimal treatment policies

Annual monitoring of quality-of-care indicators associated with and predictive of HIV drug resistance (early warning indicators of HIV drug resistance)

Surveillance of HIV drug resistance

Leveraging enablers
- Using a WHO-designated laboratory for HIV drug resistance surveillance
- Identifying and allocating resources

8.7.2 HIV drug resistance surveillance

To inform national ARV guidelines and optimal ART regimen selection, WHO recommends that countries implement periodic nationally representative HIV drug resistance surveys among different populations, including adults, children and adolescents. Surveillance of HIV drug resistance provides countries with evidence that can be used to optimize ARV drug regimens at the population level for both HIV prevention and treatment.

WHO provides detailed guidance on HIV drug resistance survey methods *(16)*.

The HIV drug resistance surveys allow nationally representative assessments of the prevalence of HIV drug resistance among various populations:

- **surveillance of acquired HIV drug resistance in populations receiving ART** (adults and children): provide critical information assessing an ART programme's performance in achieving viral load suppression targets and provide robust estimates of HIV drug resistance among people whom ART has failed. This information is critical to support the selection of second-line and potentially third-line regimens *(17)*;
- **surveillance of pretreatment HIV drug resistance among treatment-naive infants newly diagnosed with HIV:** generates information to support optimal choice of first- and second-line ART regimens for children *(18)*;
- **surveillance of pretreatment HIV drug resistance among adults initiating first-line ART:** informs the selection of optimal nationally recommended first-line ART regimens and regimens used for pre- and post-exposure prophylaxis *(19)*; and
- **surveillance of HIV drug resistance among PrEP users diagnosed with HIV:** informs the selection of maximally effective first-line ART combination for PrEP users who acquire HIV and assess potential cross-resistance to ARV drugs used for PrEP and ART *(13)*. This survey type is especially relevant in countries scaling up PrEP.

Countries performing HIV drug resistance surveys are encouraged to perform HIV drug resistance testing at a WHO-designated laboratory. These laboratories are members of the WHO HIVResNet and undergo a rigorous quality assurance process and participate in annual proficiency panel testing. Overall these laboratories function under the WHO HIV drug resistance laboratory operational framework which guarantees quality-assured results for the purpose of public health surveillance *(20)*.

WHO has developed an HIV drug resistance database as a global repository of HIV drug resistance survey data, which includes deidentified individual-level epidemiological information linked to HIV genome sequences. The database supports countries in the quality assurance of their epidemiological and sequence information and generates standardized resistance interpretations. Countries are encouraged to use this database for managing the data from HIV drug resistance surveys *(21)*.

Countries are encouraged to ensure prompt interpretation and dissemination of HIV drug resistance data at the national level and to WHO to inform national and global policies in a timely manner, to enable a coordinated response and to advocate for action on HIV drug resistance prevention and response.

8.7.3 Routine monitoring of quality-of-care indicators and early warning indicators of HIV drug resistance

WHO recommends assessing whether ART programmes deliver services with the quality required to minimize the emergence of HIV drug resistance. This assessment is achieved by using a set of standard quality-of-care indicators known as early warning indicators of HIV drug resistance. Early warning indicators are a subset of quality-of-care indicators that are associated with and predictive of the emergence of HIV drug resistance and should be measured at least annually at the facility level. Early warning indicators should be used to identify gaps in service delivery for which corrective actions may be taken at the ART clinic or programme level to optimize overall clinic and programme performance. Annual monitoring of early warning indicators enables measurement of degrees of improvement or decline over time, both within and between clinics.

Early warning indicators use standardized definitions and targets, which have evolved over time as programmes mature and public health actions are refined. Table 8.2 describes the most updated set of early warning indicators of HIV drug resistance included in the 2020 WHO consolidated HIV strategic information guidelines *(1)*. The same performance strata of the early warning indicators apply to ART for children. Adults and children should be monitored separately since the determinants and responses may be different.

Since WHO recommends annual monitoring of early warning indicators at all ART clinics, in practice, they should be integrated into routine monitoring and evaluation systems of ART programmes, to minimize costs and strengthen existing data collection and reporting processes. In countries in which routine monitoring in all facilities is not implemented or not reliable, early warning indicators can be monitored through a sample of clinics that are randomly selected so that data generated from the selected facilities can be generalized and extrapolated to the national level.

Table 8.2 WHO-recommended quality-of-care indicators: early warning indicators of HIV drug resistance

Reference number[a]	Name	Description	Performance strata Green: good Amber: fair Red: poor
AV.2	Total attrition from ART	Number and percentage of people living with HIV reported to be receiving ART at the end of the last reporting period and/or newly initiating ART during the current reporting period who were not receiving ART at the end of the reporting period	Green: <15% Amber: 15–25% Red: >25%
AV.3	People living with HIV who have suppressed viral load	Percentage of people living with HIV receiving ART (for at least six months) who have suppressed viral loads (defined as viral load <1000 copies/mL)	Green: ≥90% Amber: 80 to <90% Red: <80%
AV.6	Viral load testing coverage	Percentage of people receiving ART (for at least six months) with viral load test results	Green: >95% Amber: 85–95% Red: <85%
AV.8	Appropriate second viral load test	Percentage of people receiving ART with viral load ≥1000 copies/mL who received a follow-up viral load test within six months after enhanced adherence counselling	Green: ≥90% Red: <90%
AV.10	ARV medicine stock-out	Percentage of months with any day(s) of stock-out of any routinely dispensed ARV drug during the reporting period (12 months)[b]	Green: 0% Red: >0%
AV.11	ART adherence proxy (ARV refills)	Percentage of people receiving ART who pick up all prescribed ARV drugs on time (no more than two days late at the first drug pick-up after a defined baseline pick-up)	Green: >90% Amber: 80–90% Red: <80%
AV.14	Appropriate switch to second-line ART	Percentage of patients with confirmed failure to suppress viral loads who switch to second-line ART within 90 days	Green: 100% Red: <100%

[a] Source: *Consolidated HIV strategic information guidelines: driving impact through programme monitoring and management (1).*

[b] Note that the indicator ARV medicine stock-out is described as a national indicator in the WHO consolidated HIV strategic information guidelines *(1)* as follows: % of ART sites that had stock-outs of any ARV drugs during the reporting period.

Comprehensive information on HIV drug resistance is available on the WHO website *(22)*.

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PUBLICATION, DISSEMINATION AND EVALUATION

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9. PUBLICATION, DISSEMINATION AND EVALUATION

9.1 Publication

These guidelines will be updated in full or in part based on regular scoping exercises of available evidence and experience from country implementation that will guide and trigger the need for new guidance. As the evidence base or user needs change, consideration will be given to producing technical updates on specific subjects.

The guidelines will be disseminated electronically on the WHO HIV/AIDS website and made available as a print publication on demand. Supplementary materials will be forthcoming. Dissemination will be supported by publication of selected systematic reviews and evidence in peer-reviewed journals.

9.2 Dissemination and implementation

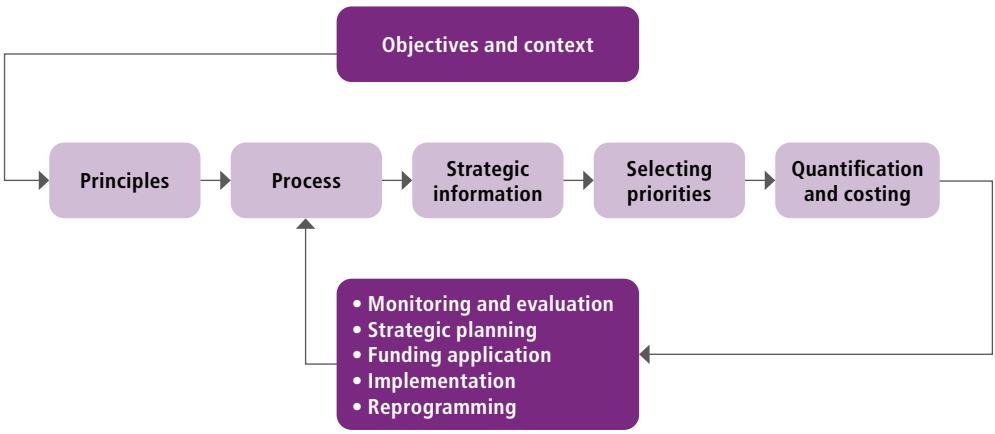
WHO headquarters will work closely with regional and country offices and implementing partners to ensure communication and country adaptation of the guidelines through regional and subregional meetings. As countries consider how to optimally implement these guidelines, the budgetary, human resource requirements and other health system implications should be analysed to identify which inputs and systems are currently available and areas that require additional investment. The implementation considerations included with each recommendation should be referred to in this process. All decisions should be made through open and informed processes involving all stakeholders and the meaningful engagement of people living with HIV. Broad stakeholder engagement in policy design, implementation, monitoring and evaluation will help to ensure that the national adaptation of these guidelines results in HIV programmes that are legitimate, acceptable, effective and equitable and address community needs.

National treatment, care and support responses need to be considered within the broader health and development context. The sustainability and effectiveness of HIV programmes can be greatly enhanced by creating and strengthening links with other health and non-health programmes to achieve broad development gains *(1)*. HIV programmes also need to be integrated into the broader health programmes and data recording and reporting systems. National programmes need to identify an essential package of high-impact HIV interventions that cover the full continuum of HIV prevention, diagnosis, treatment and care services, include it in the national health benefit package and fund it at least partly through the national health financing system. The package needs to be adapted for different populations, locations and settings and regularly reviewed and updated as necessary. Using a minimum data set with priorities set that measures the use and outcomes of these services is central to building stronger, more efficient and more effective health information systems to support the HIV response. Since funding and implementing the full range of interventions and services immediately may not be possible, an approach of progressively realizing and phasing in essential interventions should be adopted, progressively expanding the range of services offered and the populations covered and reducing out-of-pocket expenses for the users.

The recommendations included in these guidelines will need to be considered within the context of the full range of HIV interventions and services and, more broadly, the overall national health benefit package. Where dedicated national HIV budgets exist, then priorities will need to be set across all HIV interventions. Where there is no dedicated national HIV budget, then the priority of HIV interventions will need to be considered across all "essential" health interventions. To assist with this, there needs to be a clear set of criteria that can be used within the range of HIV interventions and services and more broadly for the whole national health benefit package.

WHO has developed a framework to assist the sequencing of implementation for HIV and other similar communicable disease programmes (Fig 9.1). The framework provides a structured approach to implementation considerations in the context of programme needs and available resources.

Fig. 9.1 A logical framework for implementing policies in health and HIV



The ultimate aim of selecting, adapting and implementing the recommendations in these guidelines is to reach and sustain universal coverage of the services to have the greatest impact on the epidemic. Countries are therefore encouraged to set ambitious targets and make every effort to reach them. However, disparities in coverage of services, capacity limitations, resource considerations and quality concerns often require a phased approach or sequencing to implement new recommendations. Sequencing should ensure that the implementation of each recommendation builds on another to achieve sustained scale-up and high-quality services.

9.3 Useful analytical tools for planning

Estimating the potential impact and costs associated with implementing new recommendations is a key step in the roll-out process. Several costing tools and resources are available to assist countries in estimating the costs and budgeting of HIV and related interventions and services as outlined below.

Spectrum is a suite of models and analytical tools to support decision-making *(2)*. It comprises several software applications including AIM (AIDS Impact Model) and Goals (Cost and Impact of HIV Interventions). The AIM and Resource Needs modules can be used to estimate how key new recommendations will affect the number of people dying from AIDS-related causes, the number of infants acquiring HIV and treatment needs and costs. The key data needed to generate these estimates are demographic projections, incidence trend and historical data on the numbers of people receiving ART and the unit costs and the numbers of pregnant women receiving interventions to prevent the mother-to-child transmission of HIV and the unit costs. All countries already have AIM files prepared as part of their national epidemiological estimates, so interested countries could rapidly apply both modules.

The Goals module can be used to estimate the number of adults who avoided acquiring HIV through ART under various eligibility criteria and rates of scale-up. The key inputs required are the distribution of the adult population by risk group (such as stable couples, those with casual partners, female sex workers, male clients of sex workers, men who have sex with men, transgender people and people who inject drugs); sexual behaviour by risk group (numbers of partners per year, acts per partner and condom use) and needle sharing among people who inject drugs.

OneHealth is a software tool designed to strengthen health system analysis and costing and to develop funding scenarios at the country level. It is specifically designed to assess health investment needs in low- and middle-income countries and provides planners with a single framework for planning, costing, impact analysis, budgeting and funding of strategies for all major diseases and health system components. Both Spectrum and OneHealth are available for download free of charge *(3)*.

WHO and collaborating organizations have recently developed a variety of tools to assist in drug quantification and supply management. Several are available for download *(4–6)*, with a description of their main purposes and programmatic focus. A flexible tool for costing investments in critical enablers (such as integrated treatment and rights literacy programmes, legal services, stigma and discrimination reduction programmes, training for health-care workers and law enforcement) has also been developed *(7,8)*.

Optima HIV is a tool for epidemic projection and setting priorities for the HIV response as well as evaluation. Optima is a mathematical model of HIV transmission and disease progression integrated with an economic and financial analysis framework and a formal mathematical optimization routine. The key data needed to generate these epidemiological and optimized allocation estimates are demographic, behavioural, programmatic and costing trends. Analysis determines the optimized approach to get as close as possible to defined objectives (such as national strategic plan targets) within political, ethical and logistical constraints, with the common target of minimizing the number of people acquiring HIV and dying from AIDS-related causes. The Optima HIV tool is available online free of charge *(9)*.

AIDS Epidemic Model (AEM) is a tool reflecting the primary subpopulations and transmission modes driving concentrated HIV epidemics. AEM and its associated workbooks take a mix of epidemiological, behavioural, subpopulation size and transmission-related inputs to reproduce the historical trends in each key population, producing a model tuned to the local epidemic context. It can then be used to build scenarios for future trends and effects based on either behavioural changes or programmatic inputs (coverage, effectiveness and unit cost). The AEM set of tools enables the costs and impact of different responses to the epidemic to be assessed for strategic planning *(10,11)*.

9.4 Evaluation

This guideline will be evaluated, building on the 2015 evaluation surveys, to identify the uptake of the recommendations in the guidelines into national policies and programmes. Data will be made available within the WHO country intelligence database, which is updated every six months to reflect both change in policy and implementation diffusion for all low- and middle-income countries and selected high-income countries *(12)*.

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GLOSSARY

A public health approach A public health approach addresses the health needs of a population or the collective health status of populations rather than focusing primarily on managing individual cases. This approach aims to ensure the widest possible access to high-quality services at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings. For HIV treatment, key elements of a public health approach include: using simplified drug formularies; using fixed-dose combinations on a large scale for first-line treatment for adults, adolescents and children; providing care and drugs free of user charges at the point of service delivery; decentralizing and integrating services, including task sharing; and using simplified and standardized approaches to clinical monitoring.

Acute (HIV) infection Acute HIV infection is the period between a person being infected with HIV and HIV antibodies being detectable by a serological assay.

Acquired (HIV) drug resistance Acquired HIV drug resistance develops when HIV mutations emerge from viral replication among individuals receiving ARV drugs.

Adherence Adherence is the extent to which a person's behaviour – such as taking medication, following a diet and/or changing lifestyle – corresponds with agreed recommendations from a health-care provider.

Advanced HIV disease For adults, adolescents and children five years and older, advanced HIV disease is defined as a CD4 cell count <200 cells/mm^3 or a WHO clinical stage 3 or 4 event at presentation for care. At presentation, all children living with HIV younger than five years should be considered as having advanced HIV disease.

Age groups The following definitions for adults, adolescents, children and infants are used in these guidelines for the purpose of implementing recommendations for specific age groups. It is acknowledged that countries may have other definitions under national laws:

- An adult is a person older than 19 years of age.
- An adolescent is a person 10–19 years of age inclusive.
- A child is a person one year to younger than 10 years of age.
- An infant is a child younger than one year of age.

ART (antiretroviral therapy) ART refers to using a combination of ARV drugs for treating HIV infection.

ARV (antiretroviral) ARV drugs refer to the medicines used to treat HIV.

Combination prevention Combination prevention refers to a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

Community health workers Community health workers are health workers who have received standardized and nationally endorsed training outside the nursing, midwifery or medical curricula.

Differentiated service delivery An approach that simplifies and adapts HIV services to better serve the needs of people living with HIV and to optimize the available resources in health systems.

HIV HIV refers to the human immunodeficiency virus. There are two types of HIV: HIV-1 and HIV-2. The vast majority of HIV infections globally are HIV-1.

Infant diagnosis Infant diagnosis is the testing of infants and children to determine their HIV status following possible exposure to HIV during pregnancy, delivery and postpartum. Early infant diagnosis is the testing of HIV-exposed infants before two months of age, to establish timely diagnosis and access to life-saving HIV treatment. Infant diagnosis should be performed using molecular (nucleic acid) technologies at younger than 18 months; serological assays can be used for children older than 18 months of age.

Integrated service delivery Integrated health services are health services that are managed and delivered in a way that ensures that people receive a continuum of health promotion, disease prevention, diagnosis, treatment, disease management, rehabilitation and palliative care services at the different levels and sites of care within the health system and according to their needs throughout the life-course.

Key populations Key populations are groups that have a high risk and disproportionate burden of HIV in all epidemic settings. They frequently face legal and social challenges that increase their vulnerability to HIV, including barriers to accessing HIV prevention, diagnosis, treatment and other health and social services. Key populations include men who have sex with men, people who inject drugs, people in prisons and closed settings, sex workers and transgender people.

Lay provider A lay provider is any person who performs functions related to health-care delivery and has been trained to deliver specific services but has not received a formal professional or paraprofessional certificate or tertiary degree.

Low-level viraemia Low-level viraemia is one or more viral load results that are detectable (more than 50 copies/ml) but equal to or less than 1000 copies/ml.

Midwives Midwives are health-care workers who have successfully completed a midwifery education programme recognized in the country in which the programme is located, including registered midwives, community midwives and nurse-midwives.

Non-physician clinicians Non-physician clinicians are professional health-care workers who are capable of many of the diagnostic and clinical functions of a physician but are not trained as physicians. These types of health-care workers are often known or as health officers, clinical officers, physician assistants, nurse practitioners or nurse clinicians and are an important cadre for HIV care and treatment in some countries.

Nurses Nurses are people who have been authorized to practise as a nurse or trained in basic nursing skills, including registered nurses, clinical nurse specialists, licensed nurses, auxiliary nurses, dental nurses and primary care nurses.

People-centred care People-centred care is care that is focused and organized around the health needs and expectations of people and communities rather than diseases.

Point-of-care testing Point-of-care testing is conducted at the site at which clinical care is being provided, with the results being returned to the person being tested or caregiver on the same day as sample collection and test to enable clinical decisions to be made in a timely manner.

Pretreatment drug resistance Pretreatment drug resistance refers to resistance detected among ARV drug–naive people initiating ART or people with previous ARV drug exposure initiating or reinitiating first-line ART. It can result from either transmitted or acquired HIV drug resistance, or both. Pretreatment drug resistance may have been transmitted at the time of infection (transmitted drug resistance) or may be acquired from previous ARV drug exposure (such as among women exposed to ARV drugs for preventing mother-to-child transmission of HIV, among individuals reinitiating first-line ART after a period of treatment interruption without documented viral failure or among people who have received pre-exposure prophylaxis (PrEP)).

PrEP (pre-exposure prophylaxis) HIV PrEP is the use of ARV drugs by people who are not infected with HIV to prevent the acquisition of HIV.

Rapid ART initiation Rapid ART initiation is initiation of ART within seven days of HIV diagnosis.

Retention Retention in care refers to the percentage of adults and children living with HIV and receiving ART during a specified follow-up period (12, 24, 36 months etc.).

Substantial risk (of HIV infection) Substantial risk of HIV infection is provisionally defined as an incidence of HIV greater than 3 per 100 person-years in the absence of PrEP. Individual risk varies within groups at substantial risk of HIV infection depending on individual behaviour and the characteristics of sexual partners. People at substantial risk of HIV infection are present in most countries, including some (but not all) people identified within key and vulnerable populations and some people not identified as such.

Task sharing Task sharing is the rational redistribution of tasks between cadres of health-care workers with longer training and other cadres with shorter training, such as lay providers.

Viral suppression Viral suppression is a viral load that is undetectable (less than 50 copies/ml).

Virological failure Virological failure is defined by a persistently detectable viral load exceeding 1000 copies/ml after at least six months of using ART.

Vulnerable populations Vulnerable populations are groups of people that are vulnerable to HIV infection in certain situations or contexts, such as infants, children and adolescents (including adolescent girls in sub-Saharan Africa), orphans, people with disabilities and migrant and mobile workers. They may also face social and legal barriers to accessing HIV prevention and treatment. These populations are not affected by HIV uniformly in all countries and epidemics and may include key populations, indigenous people and ethnic minorities. Each country should define the specific populations that are vulnerable to their epidemic and response, based on the epidemiological and social context.

ANNEX 1: DOSAGES FOR ARV DRUGS

Dosages of ARV drugs for adults and adolescents

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir disoproxil fumarate (TDF)	300 mg once daily[a]
Tenofovir alafenamide (TAF)	10 or 25 mg once daily[b]
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400 mg or 600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days followed by 200 mg twice daily
Protease inhibitors (PIs)	
Atazanavir/ritonavir (ATV/r)	300 mg/100 mg once daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily or 600 mg + 100 mg twice daily
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of LPV/r (double-dose LPV 800 mg + ritonavir 200 mg twice daily or super boosted with LPV 400 mg/ + ritonavir 100 mg twice daily plus additional doses of RTV 300 mg twice daily), with close monitoring. In the presence of rifabutin, no dose adjustment required. Rifapentine should not be used.
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg once daily[a]
Raltegravir (RAL)	400 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of DTG (50 mg twice daily) and RAL (800 mg twice daily), with close monitoring DTG and RAL dose should remain twice daily for additional two weeks after the last dose of rifampicin. In the presence of rifabutin or rifapentine, no dose adjustment is required.

[a] DTG 50 mg and TLD (tenofovir 300 mg, lamivudine 300 mg, dolutegravir 50 mg, fixed-dose combination) can be used once daily for adolescents living with HIV weighing at least 30 kg. DTG 50-mg film-coated tablets can be used for children and adolescents weighing at least 20 kg. TDF 300 mg can be used for adolescents weighing at least 30 kg.

[b] TAF 25 mg and TAF + FTC + DTG (TAF 25 mg, emtricitabine 200 mg, dolutegravir 50 mg, fixed-dose combination) can be used once daily for adolescents living with HIV weighing at least 25 kg. The TAF dose is reduced to 10 mg when administered in the context of boosted regimens.

Weight-based dosing for ARV drug formulations for infants and children

Prescribing information and weight-based dosing of available ARV formulations for infants and children

This annex contains information on ARV drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing for infants, children and adolescents. WHO has undertaken the work to develop and update simplified guidance on ARV drugs for children through the Paediatric Antiretroviral Working Group.[1]

For simplification and ease of implementation, doses are expressed by weight band rather than per kilogram or per square metre of body surface area. When this simplified weight-band dosing was developed, the expected body surface area of children from low- and middle-income countries in each weight band was carefully considered. The primary source of information for the guidance provided is the manufacturer's package insert. This was supplemented with data from other clinical studies as well as expert paediatric pharmacology consultations. For ARV drug fixed-dose combinations, a dose-modelling tool *(1)* was used to predict the dose delivered for each component drug against the recommended dosing schedule. In some cases, the dose for a component in a particular weight band may be somewhat above or below the target dose recommended by the manufacturer. This is inevitable given the limitations imposed by a fixed-dose combination, but care was taken to minimize the number of children that would receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. Pharmacokinetic efficacy and safety studies have also confirmed the overall safety of this dosing approach. For simplification, ARV drugs no longer considered preferred or alternative options for children have been removed from the dosing guidance.

In the context of increasing implementation of HIV virological testing at birth, and the shift towards treating infants earlier in an effort to reduce early mortality, these guidelines include additional weight-based dosing guidance for term infants less than four weeks old, including those weighing 2–3 kg. However, there is limited experience with initiating treatment for neonates living with HIV younger than two weeks and a paucity of pharmacokinetic data to fully inform accurate dosing for most drugs in neonates, who are undergoing rapid growth and maturation in renal and liver function. Limited pharmacokinetic data for preterm infants are available for AZT, NVP, 3TC and ABC; there is considerable uncertainty of appropriate dosing for NVP, RAL, 3TC and ABC for preterm and low-birth-weight infants. In addition, LPV/r solution should not be given to infants younger than two weeks old or to preterm infants until they have reached 42 weeks of gestational age, because of the risk of adverse effects that may occur in this population. The management of HIV treatment for preterm neonates remains challenging because of the lack of appropriate pharmacokinetic, safety and dosing information as well as suitable formulations.

[1] Paediatric Antiretroviral Working Group members: Elaine Abrams (ICAP at Columbia University, USA); Pauline Amuge (Baylor College of Medicine Children's Foundation, Uganda); Mo Archary (University of Kwazulu-Natal, South Africa); Adrie Bekker (University of Stellenbosch, South Africa); Brookie Best (University of San Diego, USA); David Burger (Radboud University Nijmegen Medical Centre, Netherlands); Esther Casas (MSF, South Africa); Luis Castaneda (Hospital de Ninos Benjamin Bloom, El Salvador); Diana Clarke (Boston Medical Center, USA); Polly Clayden (HIV i-Base, United Kingdom); Angela Colbers (Radboud University Nijmegen Medical Centre, Netherlands); Tim R. Cressey (PHPT-IRD Research Unit, Chang Mai University, Thailand); Roberto Delisa (European Medicines Agency); Paolo Denti (University of Cape Town, South Africa); Diana Gibb (MRC Clinical Trials Unit at University College London, United Kingdom); Rohan Hazra (National Institute of Child Health and Human Development, USA); Maria Kim (Baylor International Pediatric AIDS Initiative, Malawi); Shahin Lockman (Harvard T.H. Chan School of Public Health, USA); Fatima Mir (Agha Khan University, Pakistan); Mark H. Mirochnick (Boston Medical Center, USA); Elizabeth Obimbo (University of Nairobi/Kenyatta National Hospital); Thanyawee Puthanakit (Chulalongkorn University, Thailand); Natella Rakhmanina (Elizabeth Glazer Paediatric AIDS Foundation, USA); Pablo Rojo (Hospital de 12 Octubre Madrid, Spain); Vanessa Rouzier (GHESIKO); Ted Ruel (University of California, San Francisco, USA); Nadia Sam-Agudu (Institute of Human Virology, Nigeria); Mariam Sylla (EVA Network, Mali); and Anna Turkova (MRC Clinical Trials Unit at University College London, United Kingdom).
Observers: Yodit Belew (United States Food and Drug Administration, USA); Helen Bygrave (Access Campaign MSF); Shaffiq Essajee (UNICEF, USA); Stephanie Hackett (United States Centers for Dsiease Control and Prevention, USA); Marc Lallemant (PHPT Foundation, Thailand); Linda Lewis (Clinton Health Access Initiative, USA); Lynne Mofenson (Elizabeth Glaser Paediatric AIDS Foundation, USA); Irene Mukui (Drugs for Neglected Diseases initiative, Geneva, Switzerland); Sandra Nobre (Medicines Patent Pool, Switzerland); Mary Ojoo (UNICEF, Denmark); George Siberry (United States Agency for International Development, USA); Nandita Sugandhi (ICAP at Columbia University, USA); Marissa Vicari (International AIDS Society, Switzerland); Melynda Watkins (Clinton Health Access Initiative, USA); and Hilary Wolf (Office of the United States Global AIDS Coordinator, Department of State, USA).

Dosing for postnatal prophylaxis for infants exposed to HIV is also included here. These guidelines provide simplified dosing to administer enhanced or extended prophylaxis with NVP 50 mg scored dispersible tablets, which provide an alternative to NVP syrup. Finally, alternative ARV drugs were considered to address special situations in which stock-outs of NVP or AZT may affect the ability to effectively provide postnatal prophylaxis (including for enhanced and extended prophylaxis).

Since the WHO ARV drug guidelines were revised in 2018, integrase strand transfer inhibitors (INSTIs) have been included more prominently among the preferred regimens recommended by WHO, and DTG-based regimens have been recommended for all children with approved DTG dosing. At the time of this update in July 2021, the United States Food and Drug Administration and the European Medicines Agency have approved DTG for treatment-naive or treatment-experienced INSTI-naive children who are at least four weeks old and weigh at least 3 kg *(2,3)*. These approvals were granted based on data generated by the IMPAACT P1093 registration trial *(4)* as well as the multicountry Odyssey trial *(5)*, which also investigated the pharmacokinetics of DTG among children co-treated for TB.

- In November 2020, the United States Food and Drug Administration approved the first generic DTG 10 mg scored dispersible tablet. DTG dispersible tablets should be ideally dispersed in water or swallowed whole. Crushing, chewing or mixing with other foods or liquids can be considered as long as the entire tablet is ingested. DTG dispersible tablets are not bioequivalent to DTG film-coated tablets; 30 mg of DTG dispersible tablet is equivalent to 50 mg of DTG film-coated tablets *(6)*.
- For infants who received RAL-containing ART for limited duration (such as no more than three months) and without evidence or suspicion of treatment failure, the Paediatric Antiretroviral Working Group concluded that switching to standard (once-daily) weight-appropriate DTG was reasonable while encouraging the generation of direct evidence to evaluate this approach. Of note, although DTG can be dosed twice daily for treating adults with suspected INSTI resistance, this approach cannot be safely extrapolated to children given differences in pharmacokinetics. Alternative regimens should be considered and, if possible, informed by appropriate HIV drug resistance testing.
- This annex includes guidance on dose adjustment for children receiving a DTG formulation during rifampicin-based TB co-treatment. For all weights and ages with approved DTG dosing, the United States Food and Drug Administration recommended administering the weight-based DTG dose twice daily if taken with rifampicin based on its customary approach of extrapolating drug–drug interaction data from adults. Direct pharmacokinetic data for children support the use of DTG twice daily for children weighing more than 25 kg *(7)*. The DTG dose will need to remain twice daily for two weeks after the last dose of rifampicin has been given since the enzyme-inducing effect of rifampicin slowly fades away after discontinuing the drug. The Paediatric Antiretroviral Working Group highlights the need to continue to collect confirmatory evidence in lower weight bands but, as reflected in the dosing table, endorses immediate uptake of twice-daily dosing of DTG when taken with rifampicin for all children (at least four weeks old and weighing at least 3 kg) and to be continued for two weeks after cessation of rifampicin-based TB treatment.

RAL granules were added in 2018 with the goal of providing a suitable formulation to deliver RAL to neonates. Because of concerns about the complexity of administering the granule formulation, the Paediatric Antiretroviral Working Group endorsed the 25-mg chewable tablets as dispersible tablets for infants and children older than four weeks and weighing at least 3 kg. This decision was largely based on in vitro data on solubility and bioequivalence between RAL chewable tablets and granules *(8)* and considering the limited availability of alternative formulations for this age group. In this update of the dosing guidance, we also recommend appropriate dose adjustment for of RAL during rifampicin-based TB treatment, to be continued for two weeks after completion of rifampicin-based TB treatment.

In this 2021 update, we confirm dosing information for children for tenofovir alafenamide (TAF), fixed-dose combinations containing TAF were included for children weighing 25 kg or more with a 25-mg dose when used with unboosted regimens. This aligns with dosing approved by United States Food and Drug Administration *(9)*. Studies to investigate dosing for children weighing less than 25 kg are ongoing, and more information will be made available as soon as approval is extended.

This dosing annex and the simplified dosing schedule will be regularly reviewed and updated as additional data and new formulations become available. Updated information on ARV drug dosing in children and rationale for dose simplification is available on the newly developed paediatric ARV dosing dashboard *(10)*.

ARV drugs and formulations are available from several manufacturers, and the available dosage strengths of tablets, capsules and liquid formulations may vary from the information provided here. Several optimal dosage forms for children are currently being developed but have not yet received regulatory approval at the time these updated guidelines were published. National programme managers should ensure that products planned for use have received stringent regulatory approval and are of appropriate quality and stability. The current list of WHO prequalified drugs is available *(11)*. The United States Food and Drug Administration has a current list of approved and tentatively approved ARV drugs *(12)*. The policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria on procurement and quality assurance is available *(13)*.

General principles

WHO followed the following principles in developing the simplified tables.

- Using an age-appropriate fixed-dose combination is preferred for any regimen if such a formulation is available.
- Oral liquid or syrup formulations should be avoided if possible (except for neonatal treatment and prevention). Dispersible tablets (or granules) are the preferred solid oral dosage forms, since these formulations can be made into liquid at the point of use.
- If suitable dispersible fixed-dose combinations are not available and oral liquids must be used, children should be switched to a solid oral dosage form as soon as possible.
- Although dosing newborns generally requires using oral liquid formulations for administrating precise dosing, switching to solid oral dosage form as soon as possible is recommended.
- If children have to use adult formulations, care must be taken to avoid underdosing and overdosing. Using scored tablets is preferred to ensure accurate dosing, especially if adult dosage forms are used. Splitting unscored tablets should be avoided since the uniform distribution of active drug product cannot be assured in tablet fragments.
- Some tablets such as LPV/r or ATV/r heat-stable tablets are made in a special embedded matrix formulation (a proprietary melt extrusion technology that stabilizes drug molecules that are normally heat labile) and should not be cut, split, dissolved, chewed or crushed, since bioavailability is significantly reduced when they are not swallowed whole.
- Among children for whom an LPV/r-based regimen remains the appropriate treatment choice, LPV/r is available in a 40 mg/10 mg pellet or granule formulation for infants and young children. However, children weighing 10 kg or more should be transitioned to LPV/r heat-stable tablets as soon as they are able to swallow tablets whole to ease administration and improve palatability and to reduce pill burden.
- After the first four weeks of life, at each clinic visit, infants and children should be weighed and doses should be adjusted based on observed growth and change in body weight.
- Country programmes should consider the national regulatory status and local availability status of specific dosage forms when developing national recommendations for treating children.
- Research is ongoing for several ARV medications to establish dosing guidance for neonates, infants and young children. The age indications for each drug mentioned in the drug pages are based on current evidence and will be updated as new recommendations become available.

Table A1.1 Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children four weeks and older[a]

Drug	Strength of paediatric tablets	Number of tablets by weight band morning and evening										Strength of adult tablet	Number of tablets by weight band	
		3–<6 kg		6–<10 kg		10–<14 kg		14–<20 kg		20–<25 kg			25–<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg[b]	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/300 mg	0.5	0.5
	Tablet (dispersible) 120 mg/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 mg/300 mg	0.5	0.5

[a] For infants younger than four weeks old, see Table A1.4 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, the immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

[b] This formulation will be phased out of use over time, and programmes should transition to using the 120 mg/60 mg dispersible scored tablets.

Table A1.2 Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older[a]

Drug	Strength of paediatric tablet	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets or capsules by weight band once daily
		3–<6 kg	6–<10 kg	10–<14 kg	14–<20 kg	20–<25 kg		25–<35 kg
EFV[b]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	-	2
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	2	3	4	5	6	600 mg/300 mg	1
	Tablet (dispersible) 120 mg/60 mg	1	1.5	2	2.5	3		
TAF/FTC[c]	Tablet 25 mg/ 200 mg	–	–	–	–	–	25 mg/200 mg	1
ATV[d]	Capsules 100 mg	–	–	2	2	2	300 mg	1[e]
	Capsules 200 mg	–	–	1	1	1		
DRV[f]	Tablet 600 mg	–	–	–	1	1	600 mg	1
	Tablet 150 mg	–	–	–	4	4		
RTV[g]	Tablet 25 mg	–	–	–	4	4	100 mg	1
	Tablet 50 mg	–	–	–	2	2		

Table A1.2 Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older[a] (continued)

Drug	Strength of paediatric tablet	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets or capsules by weight band once daily
		3–<6 kg	6–<10 kg	10–<14 kg	14–<20 kg	20–<25 kg		25–<35 kg
DTG[h]	Film-coated tablet 50 mg	–	–	–	–	1	50 mg	1
	Dispersible tablet 5 mg	1	3	4	5	6		
	Dispersible scored tablet 10 mg	0.5	1.5	2	2.5	3		

[a] See Table A1.4 for dosing recommendations for infants younger than four weeks old. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

[b] EFV is not recommended for children younger than three years and weighing less than 10 kg.

[c] At the time of this update, the United States Food and Drug Administration approved TAF film-coated tablets for children older than six years for use in unboosted regimens such as with DTG. The United States Food and Drug Administration tentatively approved a fixed-dose combination containing TAF/FTC/DTG (TAF 25 mg, FTC 200 mg, DTG 50 mg) that can be used once daily for children and adolescents living with HIV weighing at least 25 kg.

[d] ATV is only approved for children three months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands 10 kg and above. ATV powder formulation has limited availability in low- and middle-income countries but enables ATV to be administered to infants and children as young as three months. Infants and children weighing 5–<15 kg should be administered 200 mg of ATV powder (four packets, 50 mg per packet) with 80 mg of RTV oral solution (1 mL) *(14)*.

[e] ATV 300 mg with RTV 100 mg for 25–<30 kg is recommended based on the findings from the PRINCE-2 study *(15)*.

[f] DRV in combination with RTV should be used for children older than three years, once daily when this is used without previous exposure to PIs. Although the approved dosing for 30–<35 kg is 675 mg, preliminary data from adult studies suggest that even lower DRV doses may be effective, and the 600 mg dose was therefore extended to the entire 25- to <35 kg weight band.

[g] RTV should only be use as a boosting agent in combination with ATV or DRV or to super-boost LPV/r when given with concomitant rifampicin for TB (see Table A1.5).

[h] At the time of this update, the United States Food and Drug Administration approved 5 mg dispersible tablets and tentatively approved 10-mg scored dispersible tablets for treatment-naive or treatment-experienced INSTI-naive children at least four weeks old and weighing at least 3 kg, based on data from the IMPAACT 1093 trial *(4)* and ODYSSEY *(16)*. The United States Food and Drug Administration and European Medicines Agency approved simplified dosing of the DTG 50 mg film-coated tablets for all children weighing ≥20 kg. DTG dispersible tablets and DTG film-coated tablets are not bioequivalent; 30 mg of DTG dispersible tablet corresponds to 50 mg of DTG film-coated tablets. DTG 50 mg film-coated tablets are preferred for children who have reached 20 kg (unless they cannot swallow tablets). Safety monitoring remains important given the current limited experience with this dosing. For adolescents living with HIV weighing more than 30 kg, a fixed-dose formulation of TDF 300 mg, 3TC 300 mg and DTG 50 mg (TLD) can be used and is preferred.

Table A1.3 Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children four weeks of age and older[a]

Drug	Strength of paediatric tablets	Number of tablets or mL by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3–<6 kg		6–<10 kg		10–<14 kg		14–<20 kg		20–<25 kg			25–<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
LPV/r[b]	Tablet 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	–	3	3
	Pellets 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6		–	–
	Granules 40 mg/10 mg sachet	2	2	3	3	4	4	5	5	6	6		–	–
DRV[c]	Tablet 75 mg	–	–	–	–	–	–	5	5	5	5	400 mg	1	1
RTV[d]	Tablet 25 mg	–	–	–	–	–	–	2	2	2	2	100 mg	1	1
	Tablet 50 mg	–	–	–	–	–	–	1	1	1	1			
RAL[e]	Chewable tablets 25 mg	1	1	2	2	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5			

Table A1.3 Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children four weeks of age and older[a] (continued)

Drug	Strength of oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3–<6 kg		6–<10 kg		10–<14 kg		14–<20 kg		20–<25 kg			25–<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Liquid formulations														
AZT	10 mg/mL	6 mL	6 mL	9 mL	9 mL	12 mL	12 mL	–	–	–	–	–	–	–
ABC[f]	20 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
3TC	10 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
LPV/r[b]	80 mg/20 mg/mL	1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.5 mL	2.5 mL	3 mL	3 mL	–	–	–
DRV[c]	100 mg/mL	–	–	–	–	2.5 mL	2.5 mL	3.5 mL	3.5 mL	–	–	–	–	–
RTV[d]	80 mg/mL	–	–	–	–	0.5 mL	0.5 mL	0.6 mL	0.6 mL	–	–	–	–	–
RAL[e]	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)	3 mL	3 mL	5 mL	5 mL	8 mL	8 mL	10 mL	10 mL	–	–	–	–	–

[a] See Table A1.4 for dosing recommendations for infants younger than four weeks. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the dosing of ARV drugs for preterm and low-birth-weight infants.

[b] Although ABC dose represents a significant increase compared with the neonatal dose, this dose was designed to match the recommended dose for the solid formulation above.

[c] LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. Adult 200/50 mg tablets could be used for children weighing 14–<25 kg (one tablet in the morning and one in the evening) and for children weighing 25–<35 kg (two tablets in the morning and one in the evening). The LPV/r pellet formulation should not be used for infants younger than three months. More details on the administration of LPV/r pellets are available *(17)*. This dosing schedule applies to equivalent solid dosage forms such as LPV/r granules, which can be used from two weeks of age. Since the supply is currently constrained, both pellets and granules should be discouraged for children weighing more than 14 kg, who should receive LPV/r 100/25 mg tablets instead. Information on LPV/r formulations for children is available *(18)*.

[d] DRV to be used for children older than three years must be administered with 0.5 mL of RTV 80 mg/mL oral suspension if they weigh less than 15 kg and with RTV 50 mg (using 25 mg or 50 mg solid formulation) for children weighing 15–<30 kg. RTV 100-mg tablets can be used as a booster if lower-strength RTV tablets are not available, based on limited experience suggesting good acceptability and tolerability.

[e] RTV should only be used at this dose as a boosting agent in combination with ATV or DRV.

[f] RAL granules are approved from birth. The feasibility and acceptability of such formulations have not been widely investigated, and concerns have been raised about administration in resource-limited settings. Because of the administration challenges presented by the granule formulation, the Paediatric Antiretroviral Working Group endorsed the use of the 25 mg chewable tablets as dispersible for infants and children older than four weeks and weighing at least 3 kg. This was largely based on in vitro data on solubility and bioequivalence between tablets and granules *(19)* and on considering the limited availability of adequate alternatives for this age group. However, the findings from a feasibility and acceptability assessment conducted in South Africa demonstrate that administering RAL granules in rural settings is feasible as long as it is supported by adequate training and counselling.

Table A1.4 Drug dosing of liquid formulations for infants younger than four weeks of age[a]

Drug	Strength of oral solution		2–<3 kg		3–<4 kg		4–<5 kg	
			AM	PM	AM	PM	AM	PM
AZT	10 mg/mL		1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL
ABC	20 mg/mL		0.4 mL	0.4 mL	0.5 mL	0.5 mL	0.6 mL	0.6 mL
NVP	10 mg/mL		1.5 mL	1.5 mL	2 mL	2 mL	3 mL	3 mL
3TC	10 mg/mL		0.5 mL	0.5 mL	0.8 mL	0.8 mL	1 mL	1 mL
LPV/r[b]	80 mg/20 mg/mL		0.6 mL	0.6 mL	0.8 mL	0.8 mL	1 mL	1 mL
	Granules 40 mg/10 mg sachet		–	–	2	2	2	2
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)[c]	<1 week	0.4 mL (once daily)[c]		0.5 mL (once daily)[c]		0.7 mL (once daily)[c]	
		>1 week	0.8 mL	0.8 mL	1 mL	1 mL	1.5 mL	1.5 mL

[a] To avoid dose changes over a short period of time and to minimize the likelihood of errors, all ARV drugs except for RAL (dose change after week 1), should be dosed based on weight when treatment starts and maintained until four weeks of age (weight gain is limited during the first four weeks of life). Pharmacokinetic data for preterm infants are available only for AZT; there are limited data and considerable uncertainty of appropriate dosing for NVP, RAL and 3TC for preterm and low-birth-weight infants. In addition, LPV/r solution should not be given to preterm infants until they have reached 42 weeks gestational age, because of the risk of adverse effects. This guidance will be updated when more evidence on solid LPV/r formulations is available from ongoing trials.

[b] Do not use LPV/r solution for infants aged younger than 2 weeks of age. LPV/r pellets should not be used for infants younger than three months. More details on administering LPV/r pellets is available *(17)*. Because of lack of clinical data to fully inform the use of LPV/r granules for newborns, these dosing recommendations were developed based on the current United States Food and Drug Administration approval (supporting use of LPV/r granules from two weeks) and considering the substantial uncertainty, especially for neonates weighing 2–3 kg. If no other formulation exists, one sachet twice a day could be considered for neonates older than two weeks who weigh 2–3 kg to minimize the risk of potential toxicity with overdosing.

[c] RAL granules for oral suspension should be used for newborns weighing at least 2 kg and be administered once a day during the first week of life and twice a day afterwards *(20)*.

Table A1.5 ARV drug dose adjustment for children receiving rifampicin-containing TB treatment[a]

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3–<6 kg		6–<10 kg		10–<14 kg		14–<20 kg		20–<25 kg			25–<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
DTG[b]	5 mg dispersible tablets	1	1	3	3	4	4	5	5	6	6	50 mg film-coated tablets	1	1
	10 mg scored dispersible tablets	0.5	0.5	1.5	1.5	2	2	2.5	2.5	3	3			
	50 mg film-coated tablets	–	–	–	–	–	–	–	–	1	1			
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)	6 mL	6 mL	10 mL	10 mL	16 mL	16 mL	20 mL	20 mL	–	–	400 mg	2	2
	Chewable tablets 25 mg	2	2	4	4	6	6	8	8	–	–			
	Chewable tablets 100 mg	–	–	–	–	–	–	2	2	3	3			
LPV/r[c] (with additional RTV)	Oral solution[d] 80/ 20 mg/mL	1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.5 mL	2.5 mL	3 mL	3 mL	–	–	–
	Pellets[e] 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	–	–	–
	Granules 40 mg/10 mg sachet	2	2	3	3	4	4	5	5	6	6	–	–	–
	Tablet 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	100 mg/25 mg	3	3

Table A1.5 ARV drug dose adjustment for children receiving rifampicin-containing TB treatment[a] (continued)

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3–<6 kg		6–<10 kg		10–<14 kg		14–<20 kg		20–<25 kg			25–<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
RTV[f]	Tablet 100 mg	–	–	–	–	1	1	1	2	1	2	100 mg	2	2
	Tablet 50 mg	–	–	–	–	2	2	3	3	3	3			
	Tablet 25 mg	–	–	–	–	4	4	6	6	6	6			
	Oral solution 80 mg/mL	0.8 mL	0.8 mL	1.2 mL	1.2 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.3 mL	2.3 mL	–	–	–
	Powder 100 mg/packet	–	–	1	1	1	1	1	2	1	2	–	–	–

[a] The adapted dose of the ARV drugs needs to continue until two weeks after rifampicin treatment ends, since the enzyme-inducing effect of rifampicin slowly fades away after discontinuing the drug.

[b] The United States Food and Drug Administration recommended administering the weight-based DTG dose twice daily if taken with rifampicin based on its customary approach of extrapolating drug–drug interaction data from adults. Direct pharmacokinetic data in children support the use of DTG twice daily for children weighing more than 25 kg *(21)*. The Paediatric Antiretroviral Working Group highlights the need to continue to collect confirmatory evidence for lower weight bands but endorses immediate uptake of twice-daily dosing of DTG when taken with rifampicin for all children (at least four weeks of age and weighing at least 3 kg).

[c] The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. An adult 200/50 mg tablet could be used for children weighing 14–<25 kg (one tablet in the morning and one in the evening) and for children 25–<35 kg (two tablets in the morning and one in the evening).

[d] LPV/r liquid requires a cold chain during transport and storage.

[e] The LPV/r pellet formulation should not be used for infants younger than three months. More details on administering LPV/r pellets is available *(17)*. The dosing schedule provided applies to equivalent solid dosage forms that may become available such as LPV/r granules, which the United States Food and Drug Administration has approved for from two weeks of life.

[f] Suggested RTV dose for super-boosting to achieve the same dose as LPV in mg, in a ratio equal or approaching to 1:1. This dosing approach is supported by a study that explored this approach for young children receiving LPV/r *(22)*. RTV oral solution dosing is based on the dosing tested in the trial that supports the use of super-boosting.

Table A1.6 Simplified dosing of isoniazid and co-trimoxazole prophylaxis for infants and children at least four weeks old

Drug	Strength of paediatric tablet or oral liquid	Number of tablets or mL by weight band once daily					Strength of adult tablet	Number of tablets by weight band
		3–<6 kg	6–<10 kg	10–<14 kg	14–<20 kg	20–<25 kg		25–<35 kg
Isoniazid	100 mg	0.5	1	1.5	2	2.5	300 mg	1
Co-trimoxazole (sulfamethoxazole and trimethoprim)	Suspension 200 mg/ 40 per 5 mL	2.5 mL	5 mL	5 mL	10 mL	10 mL	–	–
	Tablets (dispersible) 100 mg/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400 mg/80 mg	–	0.5	0.5	1	1	400 mg/80 mg	2
	Tablets (scored) 800 mg/160 mg	–	–	–	0.5	0.5	800 mg/160 mg	1
Isoniazid/ (sulfamethoxazole and trimethoprim)/ B6	Tablets (scored) 300 mg/(800 mg/ 160 mg) /25 mg	–	–	–	0.5	0.5	300 mg/ (800 mg/ 160 mg)/ 25 mg	1

Table A1.7 Simplified age-based ARV drug dosing for administering enhanced and prolonged postnatal prophylaxis[a]

Drug	Strength	0–6 weeks		6–12 weeks		12 weeks to 6 months		9–24 months	
		AM	PM	AM	PM	AM	PM	AM	PM
NVP[b]	50 mg scored dispersible tablets	0.5	_	0.5	_	0.5	_	1	_
NVP	10 mg/mL	1.5 mL	_	2 mL	_	3 mL	_	4 mL	_
AZT	10 mg/mL	1.5 mL	1.5 mL	6 mL	6 mL	_	_	_	_

[a] In special circumstances with stock-out of NVP and/or AZT, alternative ARV drugs could be used: RAL with treatment dosing, 3TC or LPV/r based on evidence gathered through the PROMISE trial: 3TC was administered as follows: 7.5 mg once daily for neonates weighing 2–<4 kg, 25 mg once daily for infants weighing 4–<8 kg and 50 mg once daily for children weighing more than 8 kg; LPV/r was administered twice daily after the first week of life according to the following dosing scheme: 40/10 mg once daily for neonates weighing 2–<4 kg and 80/20 mg once daily for infants weighing more than 4 kg *(23)*.

[b] This simplified dosing was developed with a WHO generic tool based on previously established NVP prophylactic targets.

Optimal ARV drug formulary for children

In recent years, a number of improved ARV drug formulations have become available, such as dispersible, scored fixed-dose combination tablets that have replaced traditional liquid formulations. These products have greatly simplified the delivery of HIV treatment for children in low-income settings; however, the proliferation of options has resulted in a multiplicity of formulations across regimens and weight bands. Generic manufacturers use economies of scale to maintain affordable pricing, but fragmentation of demand across too many duplicative products creates instability in the reliable supply of ARV dosage forms for children and complicates procurement and supply chain management.

Partners of the ARV Procurement Working Group *(24)* and of the Global Accelerator for Paediatric Formulations Network *(16)* provide formulary guidance to programmes on selecting optimal ARV drugs for children, which have been defined using a robust set of criteria. The formulary was first developed in 2011 but is routinely revised to correspond to current WHO guidelines and available products. The current Optimal Formulary was revised in December 2020 and released in April 2021 *(25)*. It now includes seven products that deliver recommended and appropriate first and second-line regimens across all weight bands for children. Programmes are encouraged to procure dosage forms for children that are included in the Optimal ARV Formulary for Children. During periods of transition or in special circumstances (neonatal treatment, TB co-treatment and third-line ART), dosage forms included on the ARV Limited-use Formulary are sufficient to provide appropriate dosing across weight bands for children *(26)*.

The need for new formulations

As part of the Global Accelerator for Paediatric Formulations Network, the work of the Paediatric Antiretroviral Working Group and the Paediatric ARV Drug Optimization *(27,28)* groups continue to highlight the urgent need for better age-appropriate formulations for infants and children living with HIV. An additional solid fixed-dose combination formulation is under the final stage of approval (ABC/3TC/LPV/r granules). In addition, the availability of co-formulated DRV/r in a heat-stable fixed-dose combination is critical to facilitate treatment sequencing and uptake of future second- and third-line regimens for children. Several formulations containing approved ARV drugs for children have been formally given priority and are listed in Table A1.6. Finally, additional formulations containing newer drugs for which there is currently no indication for children were considered, and the central future role of DTG and TAF in optimizing dose, sequencing and harmonization across age groups was highlighted.

In moving towards promoting drug optimization for children and adolescents, WHO will continue to work to simplify prescribing, dispensing and dosing guidance and work with the pharmaceutical industry (originator and generic) and other partners to develop more practical recommendations on the range of formulations required to safely accelerate the scaling up of ART for children.

Box A1.1 Anticipated simplified dosing for formulations under development

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)											
		3–<6 kg		6–<10 kg		10–<14 kg		14–<20 kg		20–<25 kg		25–<35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC/LPV/r	30 mg/15 mg/40 mg/10 mg granules	2	2	3	3	4	4	5	5	6	6	–	
DRV/r	120 mg/20 mg tablet	–	–	–	–	2	2	3	3	3	3	4	4
ABC/3TC/DTG[a]	Dispersible 60 mg/30 mg/5 mg tablet	–		3		4		5		6		–	

[a] This dosage form is the one identified by the PADO4 group *(28)* as the most likely to deliver appropriate dose based on the best available information.

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ANNEX 2: KEY DRUG INTERACTIONS FOR ARVS

Introduction

This Annex summarises important drug-drug interactions (DDIs) between selected antiretrovirals and key co-medications. It is not intended to be exhaustive – to check for DDIs from a comprehensive list of antiretrovirals and co-medications the reader is directed to the University of Liverpool's HIV Drug Interactions[†] resource (www.hiv-druginteractions.org) and associated Android and iOS Apps (search "HIV iChart").

DDI recommendations in the Liverpool tool are graded according to:

i) strength of recommendation. Four categories are included based on traffic lights ("Red", "Amber", "Green" to guide decision-making, plus an additional "Yellow" category to indicate a theoretical DDI, considered unlikely to be clinically relevant (and effectively treated as a 'Green'), and

ii) quality of evidence upon which that recommendation is based – available in online versions only.

A "Red" symbol denotes a strong recommendation against giving the combination, whereas a "Green" symbol suggests no cause for concern from DDIs. **It is important to note that "Amber" does not mean the drug combination cannot be given.** It is a flag to indicate that additional considerations (such as monitoring for toxicity or loss of efficacy, dose adjustment, increased clinical vigilance) are necessary. In this Annex, "Amber" flags are accompanied by footnotes to indicate what those prescribing considerations should be. The decision whether or not to proceed with co-administration of "Amber" drug-pairs rests with the prescriber, and requires a weighing up of risks versus benefits. For example, in TB-HIV co-infection, key "Amber" DDIs include use of rifampicin with either dolutegravir, or raltegravir, but despite this the benefits of treatment greatly outweigh any risks, which can be mitigated by increasing the doses of each integrase inhibitor via a twice-daily regimen.

[†] The Liverpool Drug Interactions resources receive support from the Pharmaceutical industry, the British HIV Association, the European AIDS Clinical Society, the HIV Glasgow Conference. Editorial content is independent of financial support, and is overseen by an independent international Editorial Board. For details please see www.hiv-druginteractions.org. Our evaluation methodology is published in *Seden et al. PLoS One. 2017 Mar 23;12(3):e0173509.*

Abbreviations

ABC	Abacavir
FTC	Emtricitabine
3TC	Lamivudine
TAF	Tenofovir alafenamide
TDF	Tenofovir-DF
ZDV	Zidovudine
ATV/r	Atazanavir/ritonavir
DRV/r	Darunavir/ritonavir
LPV/r	Lopinavir/ritonavir
EFV	Efavirenz
NVP	Nevirapine
RPV	Rilpivirine
BIC/FTC/TAF	Bictegravir/emtricitabine/tenofovir alafenamide
DTG	Dolutegravir
RAL	Raltegravir

Colour legend

These drugs should not be co-administered

Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration

Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

No clinically significant interaction expected

Numbers indicate further information is available in the footnotes.

Table A2.1 Key drug interactions for ARVs

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Anaesthetics and Muscle Relaxants															
Ketamine							1	1	1	2	2				
Analgesics															
Aspirin (Analgesic)					3										
Buprenorphine							4	4		5					
Ibuprofen					3					6					
Methadone							7	8	9	10	10	11			
Morphine							12	12	12	13					
Paracetamol (Acetaminophen)															
Anthelmintics															
Albendazole						14	15	15	15						
Ivermectin															
Antiarrhythmics															
Amiodarone				16	17					2	2	18	19		
Flecainide								1				18			
Lidocaine (Lignocaine)							1	1	1		2				
Propafenone							20	1	20	2	2				
Quinidine				16	17					2	2	18	19		
Antibacterials															
Amikacin					21										

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Amoxicillin															
Ampicillin															
Azithromycin							22		22			18			
Bedaquiline							23	24	23	25					
Capreomycin					21										
Cefalexin															
Cefixime															
Ceftriaxone															
Clarithromycin				16	17		26	27	20	28	29	30	19		
Clofazimine							31		31						
Cycloserine															
Dapsone						32									
Delamanid							20	33	20						
Doxycycline										34	34				
Ethambutol															
Ethionamide															
Flucloxacillin	35														
Gentamicin					21										
Imipenem/Cilastatin															
Isoniazid															

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Kanamycin					21										
Levofloxacin							36		36			18			
Meropenem															
Metronidazole							37	37	38						
Moxifloxacin							39	2	39	2		18			
Penicillins															
Pyrazinamide															
Rifabutin				40			41	41	41	42		43			
Rifampicin				40		44								45	46
Rifapentine				40										47	48
Spectinomycin															
Sulfadiazine		49	49		21	14							50		
Tetracyclines															
Trimethoprim/Sulfamethoxazole						32									
Vancomycin					21	14									
Anti-coagulant and Anti-platelet															
Apixaban										2	2				
Aspirin (Anti-platelet)															
Clopidogrel	51									52	53				

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Dabigatran							54	54	54						
Dalteparin															
Edoxaban							1	1	1						
Enoxaparin															
Heparin															
Rivaroxaban										34	34				
Warfarin							55	56	56	57	58				
Anticonvulsants															
Carbamazepine							59	60	61	62	63			64	65
Clonazepam							1	1	1	2	2				
Gabapentin															
Lamotrigine							2	2	66	2					
Oxcarbazepine							67	67	67					68	69
Phenobarbital (Phenobarbitone)						69	70		70	71				68	65
Phenytoin							72		72	73	74			68	65
Valproate						75	2	2	66						
Antidepressants															
Amitriptyline									76						
Fluoxetine									31						
Lithium					49		31		31						

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Anti-diabetics															
Glibenclamide (Glyburide)							1	1	1	2	2				
Gliclazide							2	2	2	1					
Insulin															
Metformin													77	78	
Antifungals															
Amphotericin B					21	32									
Clotrimazole (topical)															
Clotrimazole (pessary, troche)															
Fluconazole						75	36		36		79	30			
Flucytosine		80	80		80	32							80		
Itraconazole				16	17		81	82	81	83			19		
Ketoconazole				16	17		84	85	86				19		
Nystatin															
Voriconazole							87	88	89	90	91				
Antimigraine Agents															
Ergotamine											2				
Antiprotozoals															
Amodiaquine						14					92				
Artemisinin							1	1	93	94	95				
Chloroquine							96		96			18	19		

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Hydroxychloroquine							76		76			18	19		
Lumefantrine							97	98	97	94	99				
Mefloquine							100	98	100	34	34				
Miltefosine															
Primaquine						14	31		31	101	101				
Proguanil							102	103	102	102	103				
Pyrimethamine															
Quinine							97	104	105	34	34	18			
Sulfadoxine															
Antipsychotics / Neuroleptics															
Fluphenazine						14	106		106						
Haloperidol												18			
Pimozide											2	18			
Quetiapine						14				2	2				
Antivirals															
Aciclovir (Acyclovir)					107										
Adefovir		49													
Daclatasvir							108			109	110				
Elbasvir/Grazoprevir															
Entecavir															
Famciclovir															

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Ganciclovir					21										
Glecaprevir/Pibrentasvir															
Ledipasvir/Sofosbuvir					111				112						
Remdesivir															
Ribavirin				113			114								
Sofosbuvir															
Sofosbuvir/Velpatasvir					17										
Valaciclovir					21										
Anxiolytics / Hypnotics / Sedatives															
Diazepam							1	1	1	115	115				
Lorazepam															
Midazolam (oral)											115				
Midazolam (parenteral)							1	1	1		115				
Beta Blockers															
Bisoprolol							116		116						
Carvedilol							116		116						
Metoprolol							116		116						
Bronchodilators															
Salbutamol															
Calcium Channel Blockers															
Amlodipine							117	118	117	2	2				

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Cancer Therapies															
Carboplatin					21	32									
Chlorambucil						14									
Cisplatin		49	49		49	14	119	119	119				120		
Cyclophosphamide						14	121	121	121	122	123				
Cytarabine						14									
Dacarbazine					124	14	121	121	121						
Daunorubicin						14	36		36						
Docetaxel						14	125	125	125	2	2	126			
Doxorubicin						127	36		36			128			
Fluorouracil						14	31		31						
Gemcitabine						14									
Ifosfamide				49	21	14	129	129	129	34	130	131	132		
Imatinib						14	125	125	125	133	134	135			
Irinotecan						14		136	136	137	137				
Mercaptopurine						14									
Mesna															
Methotrexate (Amethopterin)					21	138									
Oxaliplatin					49	14	36		36			18	139	139	
Paclitaxel						14	140	140	140	140		69	141	69	69

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Tamoxifen							142	143	142	144	144	145	141		
Vinblastine						32	146	146	146	144	144	69	141	69	69
Vincristine						32	146	146	146	144	144				
Vinorelbine							146	146	146	144	144				
Contraceptives/HRT															
Desogestrel (COC)								147	148						
Desogestrel (POP)															
Drospirenone (COC)								147	147						
Drospirenone (HRT)							149	149	149	150	150				
Dydrogesterone (HRT)							151	151	151	150	150				
Estradiol							150	150	150	150	150				
Ethinylestradiol							152	153	153	154					
Etonogestrel (implant)															
Etonogestrel (vaginal ring)							155	156	156						
Levonorgestrel (COC)								147	147						
Levonorgestrel (Emergency Contraception)										157					
Levonorgestrel (HRT)							151	151	151	150	150				
Levonorgestrel (implant)															

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Levonorgestrel (IUD)															
Levonorgestrel (POP)															
Medroxyprogesterone (depot injection)															
Medroxyprogesterone (oral)							151	151	151	150	150				
Norethisterone [Norethindrone] (COC)								158	158						
Norethisterone [Norethindrone] (HRT)							151	151	151	150	150				
Norethisterone [Norethindrone] (IM depot injection)										159					
Norethisterone [Norethindrone] (POP)															
Norgestimate (COC)								160	160						
Ulipristal										161	161				
Erectile Dysfunctional Agents															
Sildenafil (Erectile Dysfunction)							162	163	162	34	34				
Gastrointestinal Agents															
Antacids							164					165	166	167	168
Lansoprazole															
Loperamide							169	169	169						

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Omeprazole															
Pantoprazole															
Ranitidine							170					171			
Gastrointestinal Agents (anti-emetic)															
Metoclopramide									31						
Ondansetron							76		76			18			
Herbals / Supplements / Vitamins															
Ascorbic Acid (Vitamin C) [alone]															
Calcium supplements													172	173	174
Colecalciferol (Vitamin D3) [alone]															
Cyanocobalamin (Vitamin B12) [alone]															
Ferrous fumarate													175	173	176
Folic acid [alone]															
Garlic				177			177	177	177	177	177	177	177	177	
Iron supplements													175	173	176
Magnesium supplements													175	178	176
Multivitamins													179	178	180

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Phytomenadione (Vitamin K) [alone]															
Pyridoxine (Vitamin B6) [alone]															
Retinol (Vitamin A) [alone]															
Riboflavin (Vitamin B2) [alone]															
Thiamine (Vitamin B1) [alone]															
Tocopherol (Vitamin E) [alone]															
Hypertension / Heart Failure Agents															
Bendroflumethiazide															
Captopril															
Enalapril															
Hydralazine					21										
Hydrochlorothiazide															
Losartan															
Methyldopa						14									
Spironolactone															
Illicit/Recreational															
Alcohol															

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Cannabis							181			182					
Cocaine							183	184	183	185	185	18			
Ecstasy (MDMA)							184	184	184						
GHB (Gamma-hydroxybutyrate)							184	184	184						
LSD (Lysergic acid diethylamide)							184	184	184	186	186				
Methamphetamine							187	187	187						
Poppers (Amyl nitrate)															
Immunosuppressants															
Ciclosporin (Cyclosporine)				16	17		188	188	188	189	189		19		
Tocilizumab															
Lipid Lowering Agents															
Atorvastatin							190	191	192	193					
Pravastatin							194	195							
Simvastatin										193	196				
Other															
Alfuzosin										2	2				
Allopurinol															
Calcium folinate															
Colchicine							197	197	197						
Convalescent COVID plasma															
Leuprorelin															

Table A2.1 Key drug interactions for ARVs (continued)

	ABC	FTC	3TC	TAF	TDF	ZDV	ATV/r	DRV/r	LPV/r	EFV	NVP	RPV	BIC/FTC/TAF	DTG	RAL
Orlistat															
Zoledronic acid					21										
Oxytocics															
Ergometrine (Ergonovine)											2				
Mifepristone										2	2				
Misoprostol															
Oxytocin							31		31						
Parkinsonism Agents															
Carbidopa							198	198	198						
Levodopa							198	198	198						
Steroids															
Beclometasone															
Budesonide										2	2				
Dexamethasone							199	199	199	2	2		141		
Dexamethasone (low dose)										200	200				
Fluticasone										2	2				
Hydrocortisone (oral)							201	201	201	2	2				
Hydrocortisone (topical)															
Methylprednisolone							201	201	201	2	2				
Prednisolone							201	201	202	66	2				
Testosterone							201	201	201	2	2				

Table A2.2 Footnotes

Number	Interaction details
1	Coadministration may increase comedication exposure and a dose adjustment may be needed. Monitor clinical effect.
2	Coadministration may decrease comedication exposure. Monitor clinical effect and increase dose if needed.
3	No pharmacokinetic interaction expected. However, coadministration could potentially result in increased risk of nephrotoxicity. Alternatives to NSAIDs should be considered in patients at risk for renal dysfunction. If tenofovir-DF is co-administered with an NSAID, renal function should be monitored adequately.
4	Coadministration increased buprenorphine exposure. If coadministered, monitor for sedation and cognitive effects and consider a dose reduction of buprenorphine.
5	Coadministration decreased buprenorphine exposure. Dose adjustments are unlikely to be required, but consider monitoring for withdrawal symptoms.
6	Coadministration may increase ibuprofen exposure. Use the lowest recommended dose of ibuprofen particularly in patients with risk factors for cardiovascular disease, those patients at risk of developing gastrointestinal complications, patients with hepatic or renal impairment, and in elderly patients.
7	No significant pharmacokinetic interaction expected, but consider monitoring for withdrawal symptoms. However, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
8	Coadministration decreased methadone exposure by 16%. No dose adjustment is required, but consider monitoring for withdrawal symptoms.
9	Coadministration decreased methadone exposure by 53%. Monitor for withdrawal symptoms. In addition, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
10	Coadministration decreased methadone exposure. Patients should be monitored for signs of withdrawal and their methadone dose increased as required.
11	Coadministration caused a small decrease in methadone exposure. Clinical monitoring should be considered as methadone maintenance therapy may need to be adjusted in some patients. In addition, caution is recommended as both drugs have risks of QT prolongation (rilpivirine at supra-therapeutic doses).
12	Coadministration may increase exposure to the active metabolite and potentiate the effects of the opiate in the CNS. Monitor for sign of opiate toxicity.
13	Coadministration may increase morphine concentrations. Monitor for signs of opiate toxicity.
14	Potential haematological toxicity. Monitor haematological parameters.
15	No pharmacokinetic interaction is expected with a short duration treatment but the clinical effect of albendazole may be reduced when used for a long duration treatment.
16	Coadministration may increase exposure of tenofovir alafenamide. Consider using tenofovir alafenamide 10 mg once daily (where available).
17	Coadministration may increase tenofovir exposure. Monitoring of tenofovir-associated adverse reactions, including frequent renal monitoring, is recommended.

Table A2.2 Footnotes (continued)

Number	Interaction details
18	No pharmacokinetic interaction expected. However, caution is recommended as both drugs have risks of QT prolongation (rilpivirine at supra-therapeutic doses).
19	Coadministration may increase exposure of tenofovir alafenamide. The recommended dose of 10 mg tenofovir alafenamide with P-gp inhibitors is not possible with Biktarvy which is only available as a fixed dose combination containing 25 mg tenofovir alafenamide but it should be noted that tenofovir alafenamide has been associated with a large clinical safety profile.
20	Coadministration may increase comedication exposure. Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
21	Coadministration of tenofovir-DF should be avoided with concurrent or recent use of a nephrotoxic agent. If concomitant use is unavoidable, renal function should be monitored closely.
22	Coadministration may increase comedication exposure, but no a prior dose adjustment is recommended. However, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
23	Coadministration may increase comedication exposure. Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended. Coadministration for more than 14 consecutive days should be avoided.
24	Coadministration may increase comedication exposure. Use with caution and with ECG monitoring. Coadministration for more than 14 consecutive days should be avoided.
25	Coadministration decreased comedication exposure. Coadministration is not recommended.
26	Coadministration may increase clarithromycin exposure. Dose reduction of clarithromycin required in patients with impaired renal function. Caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
27	Coadministration increased clarithromycin exposure. No adjustment is required for patients with normal renal function but are recommended for patients with impaired renal function (CLcr 30-60 mL/min, dose reduce clarithromycin by 50%; CLcr less than 30 mL/min, dose reduce clarithromycin by 75%).
28	Coadministration decreased clarithromycin exposure and increased 14-OH clarithromycin exposure. The clinical significance of the decreases in clarithromycin is unknown. In uninfected individuals, 46% developed rash while receiving efavirenz and clarithromycin. Alternatives to clarithromycin, such as azithromycin, should be considered.
29	Coadministration decrease clarithromycin exposure and increased 14-OH clarithromycin exposure. Nevirapine exposure was increased. Close monitoring for hepatic abnormalities is recommended. As the clarithromycin metabolite has reduced activity, overall activity may be altered and alternatives such as azithromycin should be considered.
30	Coadministration may increase rilpivirine exposure. In addition, caution is recommended as both drugs have risks of QT prolongation (rilpivirine at supra-therapeutic doses).
31	No pharmacokinetic interaction expected. However, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
32	Potential renal and haematological toxicity. Monitor renal function and haematological parameters and consider dose reduction if required.

Table A2.2 Footnotes (continued)

Number	Interaction details
33	Coadministration may increase delamanid exposure. Caution is recommended due to the risk of QT prolongation. ECG monitoring is recommended.
34	Coadministration may decrease comedication exposure. Use with caution.
35	Potential hepatotoxicity. HLA-5701 genotyping is recommended.
36	No pharmacokinetic interaction expected. However, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
37	Disulfiram-like reactions may occur when coadministered with metronidazole as some ritonavir formulations (except tablets) contain alcohol.
38	No interaction expected with lopinavir/ritonavir tablets. Coadministration is contraindicated with lopinavir/ritonavir oral solution.
39	Coadministration may decrease moxifloxacin exposure. Monitor clinical effect and increase dose if needed. In addition, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
40	Potential decreased exposure of tenofovir alafenamide. However the intracellular tenofovir diphosphate (active entity) levels are likely to be higher than those obtained with TDF even without rifampicin, suggesting that usage of TAF 25 mg QD with rifampicin, rifabutin or rifapentine may be acceptable.
41	Coadministration increased rifabutin exposure. The US guidelines for HIV treatment recommend rifabutin 150 mg daily with a boosted protease inhibitor. Due to the limited safety data with this dose and combination, patients should be closely monitored for rifabutin-related toxicities (i.e. uveitis or neutropenia).
42	Coadministration decreased rifabutin exposure. Increase daily doses of rifabutin by 50%; consider doubling rifabutin doses in regimens where rifabutin is given two or three times a week. The clinical effect of this dose adjustment has not been adequately evaluated. Individual tolerability and virological response should be considered when making the dose adjustment.
43	Coadministration decreased rilpivirine exposure. Throughout co-administration of rilpivirine with rifabutin, the rilpivirine dose should be increased from 25 mg once daily to 50 mg once daily. When rifabutin co-administration is stopped, the rilpivirine dose should be decreased to 25 mg once daily. Note, it is recommended to maintain rilpivirine 50 mg once daily for at least another 2 weeks following cessation of rifabutin due to the persisting inducing effect upon discontinuation of a moderate/strong inducer.
44	Coadministration decreased zidovudine exposure. Coadministration is not recommended in the European product label for zidovudine, however, the US product label states that routine dose modification is not warranted.
45	Coadministration decreased dolutegravir concentrations. A dose adjustment of dolutegravir to 50 mg twice daily is recommended when coadministered with rifampicin in the absence of integrase class resistance. In the presence of integrase class resistance this combination should be avoided. Of note: a high dose of rifampicin (35 mg/kg) did not further increase the magnitude of the interaction with dolutegravir. Therefore, dolutegravir 50 mg twice daily dosing is suitable when coadministered with rifampicin dosed at 35 mg/kg. Dolutegravir 50 mg twice daily dosing should be maintained for another 2 weeks following cessation of rifampicin due to the persisting inducing effect upon discontinuation of a strong inducer.

Table A2.2 Footnotes (continued)

Number	Interaction details
46	Coadministration decreased raltegravir concentrations. The recommended dose of raltegravir when coadministered with rifampicin is 800 mg twice daily. Coadministration with once daily raltegravir is not recommended. Data from HIV/TB coinfected infants and children (aged 4 weeks to 12 years) receiving rifampicin suggest that the chewable formulation of raltegravir at a dose of 12 mg/kg twice daily safely achieved pharmacokinetic levels similar to HIV-infected children receiving the recommended dose of 6 mg/kg/dose and not on treatment for TB. RAL dose should remain twice daily for additional two weeks after the last dose of rifampicin in children.
47	Coadministration decreased dolutegravir concentrations, but trough concentrations remained above the target value. No dose adjustment of dolutegravir 50 mg once daily is needed when coadministered with once weekly isoniazid/rifapentine. However, dolutegravir 50 mg twice daily should be considered in individuals with suspicion of failure or blips.
48	Coadministration with weekly rifapentine increased raltegravir exposure. Once weekly rifapentine (for treatment of latent TB) can be used with raltegravir without dose adjustment. However, the proper dosing strategy of daily rifapentine (for treatment of active TB) is still under clinical investigation.
49	Potential renal toxicity. Monitor renal function.
50	Sulfadiazine may impair emtricitabine renal elimination. Monitor renal function.
51	Pharmacodynamic effect of clopidogrel maybe reduced. An alternative NRTI or antiplatelet agent should be considered.
52	Coadministration is not recommended. Coadministration may decrease conversion of clopidogrel to its active metabolite.
53	Coadministration may increase the amount of active clopidogrel metabolites and may increase nevirapine exposure. Use with caution and with monitoring of clinical and side effects.
54	No interaction expected when administered simultaneously, but dabigatran exposure may decrease if administered separately. Use with caution in patients with mild or moderate renal impairment as the dabigatran dose might need to be reduced. Dabigatran is not recommended in patients with severe renal impairment.
55	Coadministration may increase R-warfarin concentrations and decrease S-warfarin concentrations. The net effect of these interactions is unclear. Monitor INR
56	Coadministration may decrease warfarin concentrations. Use with caution. Increase monitoring of INR is recommended.
57	Coadministration may increase warfarin activity. Monitor INR.
58	Coadministration may alter warfarin concentrations. The nature and magnitude of any effect may change with time. Frequent monitoring of INR is recommended.
59	Coadministration may increase carbamazepine exposure and decrease atazanavir/ritonavir exposure. A dose adjustment may be needed. Monitor clinical effect.
60	Coadministration may increase carbamazepine exposure. A dose adjustment may be needed. Monitor clinical effect.
61	Coadministration may increase carbamazepine exposure and decrease lopinavir/ritonavir exposure. A dose adjustment may be needed. Monitor clinical effect. Coadministration with once daily lopinavir/ritonavir is not recommended.
62	Coadministration decreased carbamazepine and efavirenz exposure. There are no data from coadministration of higher doses of either drug. No dose recommendation can be made and alternative anticonvulsant treatment should be considered.

Table A2.2 Footnotes (continued)

Number	Interaction details
63	Coadministration may decrease carbamazepine and nevirapine concentrations. Dose adjustment may be needed due to possible decrease in clinical effect.
64	Coadministration decreased dolutegravir exposure. The recommended dose of dolutegravir is 50 mg twice daily when coadministered with carbamazepine in treatment-naive or treatment experienced, INSTI-naive patients. Alternatives to carbamazepine should be used where possible for INSTI resistant patients. Dolutegravir 50 mg twice daily dosing should be maintained for another 2 weeks following cessation of carbamazepine due to the persisting inducing effect upon discontinuation of a strong inducer.
65	Coadministration may decrease raltegravir exposure. Coadministration of once daily raltegravir (1200 mg once daily) is not recommended. If coadministration is unavoidable, raltegravir should be used as a twice daily regimen with close monitoring of antiretroviral response. Monitor raltegravir plasma concentrations (when possible).
66	Coadministration decreased comedication exposure. Monitor clinical effect and increase dose if needed.
67	Coadministration may decrease exposure of the antiretroviral drug, although to a moderate extent. A dose adjustment may be needed. Monitor clinical effect. Alternative anticonvulsants should be considered.
68	Coadministration may decrease dolutegravir exposure. The US Prescribing Information for dolutegravir advises to avoid coadministration due to insufficient data to make dosing recommendations. However, European SPC for dolutegravir recommends that dolutegravir be dosed at 50 mg twice daily, but that alternative combinations should be used where possible in INSTI-resistant patients. Dolutegravir 50 mg twice daily dosing should be maintained for another 2 weeks following cessation of the anticonvulsant due to the persisting inducing effect upon discontinuation of a strong inducer.
69	Coadministration may decrease exposure of the antiretroviral drug. Monitor response to antiretroviral therapy.
70	Coadministration may decrease exposure of the antiretroviral drug. A dose adjustment may be needed. Monitor clinical effect. Alternative anticonvulsants should be considered.
71	Coadministration may decrease phenobarbital and/or efavirenz exposure. No dose adjustment of efavirenz is needed based on DDIs studies with the strong inducer rifampicin. Monitor the therapeutic response of phenobarbital and increase dose if needed.
72	Coadministration may decrease phenytoin exposure and exposure of the antiretroviral drug. A dose adjustment may be needed. Monitor clinical effect. Alternative anticonvulsants should be considered.
73	Coadministration may increase or decrease phenytoin and/or efavirenz concentrations. No dose adjustment of efavirenz is needed based on DDIs studies with the strong inducer rifampicin. Monitor the therapeutic response of phenytoin and increase dose if needed.
74	Coadministration may decrease nevirapine concentrations. Perform therapeutic drug monitoring for nevirapine if available. Consider switching to another antiretroviral agent.
75	Coadministration may increase zidovudine exposure. Routine dose modification of zidovudine is not warranted, but monitor closely for potential toxicity of zidovudine.

Table A2.2 Footnotes (continued)

Number	Interaction details
76	Coadministration may increase comedication exposure, although to a moderate extent. However, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
77	Coadministration increased metformin exposure. Assess the benefit and risk of concomitant use of bictegravir and metformin, particularly in patients with renal impairment. Close monitoring should be considered when starting coadministration in patients with moderate renal impairment, due to the increased risk for lactic acidosis in these patients and a dose adjustment of metformin should be considered if required.
78	Coadministration increased metformin exposure. A dose adjustment of metformin should be considered when starting and stopping coadministration of dolutegravir with metformin in order to maintain glycaemic control. The US Prescribing Information suggests limiting the total daily dose of metformin to 1000 mg when starting metformin or dolutegravir. Monitoring renal function during coadministration and monitoring blood glucose when starting and stopping coadministration is recommended. As metformin is eliminated renally, patients with moderate renal impairment may be at increased risk for lactic acidosis due to increased metformin concentrations.
79	Coadministration increased nevirapine exposure by ~100% compared to historical data. Use with caution. Patients should be monitored closely for nevirapine-associated adverse events.
80	Potential haematological toxicity. Monitor haematological parameters and consider dose reduction if required.
81	Coadministration may increase itraconazole exposure. The daily dose of itraconazole should not exceed 200 mg. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
82	Coadministration may increase itraconazole exposure. Caution and close monitoring is recommended. The daily dose of itraconazole should not exceed 200 mg.
83	Coadministration decreased itraconazole exposure. Since no dose recommendation for itraconazole can be made, alternative antifungal treatment should be considered.
84	Coadministration may increase ketoconazole exposure. The daily dose of ketoconazole should not exceed 200 mg. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
85	Coadministration increased ketoconazole exposure. Caution and close monitoring is recommended. The daily dose of ketoconazole should not exceed 200 mg.
86	Coadministration increased ketoconazole exposure. The daily dose of ketoconazole should not exceed 200 mg. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
87	Coadministration of voriconazole is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. The effect of atazanavir/ritonavir on voriconazole exposure is dependent on CYP2C19 metaboliser status – exposure increased in extensive metaboliser and decrease in poor metabolisers. Patients should be carefully monitored for voriconazole-associated adverse reactions and loss of voriconazole efficacy. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
88	Coadministration of voriconazole is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.

Table A2.2 Footnotes (continued)

Number	Interaction details
89	Coadministration of voriconazole is not recommended unless an assessment of the benefit/risk to the patient justifies the use of voriconazole. Coadministration may result in bidirectional interactions leading to increased concentrations of lopinavir/ritonavir and an increase or decrease in voriconazole. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
90	Coadministration of standard doses of efavirenz and voriconazole is contraindicated. Efavirenz significantly decreases voriconazole plasma concentrations while voriconazole also significantly increases efavirenz plasma concentrations. When coadministered, the voriconazole maintenance dose must be increased to 400 mg twice daily and the efavirenz dose should be reduced by 50% (i.e., to 300 mg once daily). When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored.
91	Coadministration may increase nevirapine exposure and decrease voriconazole exposure. Patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy.
92	Coadministration decreased exposure of amodiaquine and desethylamodiaquine. This may negatively impact the effectiveness of artesunate/amodiaquine in patients receiving nevirapine. In addition, coadministration of these drugs may increase the risk of hepatotoxicity through additive toxicity. Careful clinical monitoring for efficacy and toxicity is recommended.
93	Coadministration increased comedication exposure and a dose adjustment may be needed. Monitor clinical effect.
94	Coadministration decreased comedication exposure. Use with caution.
95	Coadministration decreased exposure of artemisinin and nevirapine. Close monitoring of artemisinins and nevirapine therapeutic effect is recommended.
96	Coadministration may increase chloroquine exposure, although to a moderate extent. In addition, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
97	Coadministration may increase comedication exposure. In addition, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
98	Coadministration may increase comedication exposure. Caution and close monitoring is recommended.
99	Coadministration decreased exposure of lumefantrine and nevirapine. Use with caution.
100	Coadministration may increase comedication exposure. Caution and close monitoring is recommended as both drugs have risks of QT prolongation.
101	Coadministration could potentially increase the amount of haemotoxic primaquine metabolites. Use with caution.
102	Coadministration decreased proguanil exposure. Coadministration of atovaquone/proguanil should be avoided whenever possible. If judged clinically necessary, consider taking atovaquone/proguanil with a high fat meal to increase its bioavailability and increase the dosage if required.
103	Coadministration may decrease proguanil exposure. Coadministration of atovaquone/proguanil should be avoided whenever possible. If judged clinically necessary, consider taking atovaquone/proguanil with a high fat meal to increase its bioavailability and increase the dosage if required.
104	Coadministration may increase quinine exposure. In addition, caution is recommended as quinine has a risk of QT prolongation. ECG monitoring is recommended.

Table A2.2 Footnotes (continued)

Number	Interaction details
105	Coadministration may decrease quinine exposure and may result in suboptimal exposure of the antimalarial treatment. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
106	Coadministration may increase fluphenazine exposure. In addition, caution is recommended as both drugs have risks of QT prolongation. The European product label for fluphenazine contraindicates the concurrent use of other drugs that also prolong the QT interval.
107	Coadministration may increase concentrations of tenofovir and aciclovir.
108	Coadministration increased daclatasvir exposure. The dose of daclatasvir should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir.
109	Coadministration decreased daclatasvir exposure. The dose of daclatasvir should be increased to 90 mg once daily when coadministered with efavirenz.
110	Coadministration may decrease daclatasvir concentrations. Due to the lack of data, coadministration is not recommended.
111	Coadministration may increase tenofovir exposure, especially in the presence of ritonavir or cobicistat. For patients receiving a boosted HIV protease inhibitor, consider an alternative HCV or antiretroviral therapy. If coadministration is necessary, monitor for tenofovir-associated adverse reactions, including frequent renal monitoring. Note, coadministration of ledipasvir/sofosbuvir and tenofovir-DF with elvitegravir, cobicistat and emtricitabine is not recommended.
112	There has been a report of drug-induced liver injury manifesting as significant bilirubin rise within two weeks of starting ledipasvir/sofosbuvir while on lopinavir-containing ART. In addition, coadministration of ledipasvir/sofosbuvir and regimens containing a HIV protease inhibitor/ritonavir and tenofovir may increase tenofovir concentrations and require monitoring for tenofovir-associated adverse reactions including frequent renal monitoring.
113	Patients receiving interferon with ribavirin and NRTIs should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anaemia.
114	A substantial proportion of patients receiving atazanavir experienced significant hyperbilirubinemia and jaundice following initiation of ribavirin and PEGylated interferon for the treatment of hepatitis C.
115	Coadministration may decrease comedication exposure. Monitor clinical effect and withdrawal symptoms.
116	Coadministration may increase comedication exposure, although to a moderate extent. Monitor clinical effect. PR interval monitoring may be warranted in patients with underlying block or those with atrioventricular nodal blocking agents.
117	Coadministration is expected to increase amlodipine exposure by ~2-fold. Consider a dose reduction for amlodipine of 50%. Use with caution as both drugs prolong the PR interval. ECG monitoring is recommended.
118	Coadministration is expected to increase amlodipine exposure by ~2-fold. Consider a dose reduction for amlodipine of 50%.
119	Coadministration may increase cisplatin exposure, thus increasing the risk of nephrotoxicity. Close monitoring of renal function is recommended.
120	Coadministration may increase exposure of cisplatin and emtricitabine. Close monitoring of renal function is recommended.

Table A2.2 Footnotes (continued)

Number	Interaction details
121	Coadministration may increase the efficacy and the toxicity of the comedication. Careful monitoring of efficacy and toxicity is recommended.
122	Coadministration could either potentially increase the conversion of cyclophosphamide to the active metabolite or increase the amount of drug converted to the inactive neurotoxic metabolite. Careful monitoring of cyclophosphamide efficacy and toxicity is recommended.
123	Coadministration may decrease cyclophosphamide concentrations. Dose adjustment may be needed due to possible decrease in clinical effect.
124	Coadministration may increase tenofovir and dacarbazine exposure. No a priori dosage adjustment is recommended but renal function and haematological parameters should be monitored.
125	Coadministration may increase comedication exposure. Monitor for chemotherapy-induced toxicity.
126	Coadministration may alter docetaxel exposure. Use with caution.
127	Potential renal and haematological toxicity. Monitor renal function and haematological parameters and consider dose reduction if required. Note, US Prescribing Information for zidovudine advises to avoid concomitant use since an antagonistic relationship has been demonstrated in vitro.
128	No pharmacokinetic interaction expected. However, caution is recommended due to possible cardiac toxicities (ECG abnormalities and sometimes arrhythmias). ECG monitoring is recommended.
129	Coadministration may reduce conversion of ifosfamide to the active metabolite and thereby reduce efficacy. Use with caution.
130	Coadministration may decrease ifosfamide exposure and alter nevirapine exposure. Use with caution.
131	Coadministration may alter rilpivirine exposure. Use with caution.
132	Coadministration may alter bictegravir exposure. In addition, there is potential additive renal toxicity. Closely monitor renal function.
133	Coadministration may decrease imatinib exposure and increase efavirenz exposure. Use with caution.
134	Coadministration may decrease imatinib exposure and increase nevirapine exposure. Use with caution.
135	Coadministration may increase rilpivirine exposure. Use with caution.
136	Coadministration may increase the risk of irinotecan related toxicity. Close monitoring is recommended.
137	Coadministration may increase the conversion of irinotecan to the inactive metabolites. Monitor the clinical efficacy.
138	Potential haematological toxicity. Monitor haematological parameters. Note, some methotrexate product labels contraindicate its use or advise caution in immunodeficiency and some contraindicate its use in HIV infection.
139	Coadministration may decrease the efficacy of oxaliplatin. When possible, use raltegravir.
140	Coadministration may increase paclitaxel exposure. Monitor paclitaxel induced toxicity.

Table A2.2 Footnotes (continued)

Number	Interaction details
141	Coadministration may decrease bictegravir exposure. Use with caution.
142	Coadministration may reduce conversion to the active metabolite and thereby reduce efficacy of the comedication. Monitor response to chemotherapy. In addition, caution is recommended as both drugs have risks of QT prolongation. ECG monitoring is recommended.
143	Coadministration may reduce conversion to the active metabolite and thereby reduce efficacy of the comedication. Monitor response to chemotherapy.
144	Coadministration may decrease comedication exposure. Monitor response to chemotherapy.
145	Coadministration may decrease rilpivirine exposure. Monitor response to antiretroviral therapy. In addition, caution is recommended as both drugs have risks of QT prolongation (rilpivirine at supra-therapeutic doses).
146	Coadministration may increase comedication exposure. Monitor for chemotherapy-induced toxicity. Consider temporarily withholding the ritonavir-containing antiretroviral regimen in patients who develop significant side effects. If the antiretroviral regimen must be withheld for a prolonged period of time, consider initiating a revised regimen that does not include a CYP3A or P-gp inhibitor.
147	Coadministration may increase comedication exposure and, when used in a combined pill, the estrogen component was reduced. Given the lack of clinical data on the contraceptive efficacy, caution is recommended and additional contraceptives measures should be used.
148	Coadministration increased comedication exposure and, when used in a combined pill, the estrogen component was reduced. Given the lack of clinical data on the contraceptive efficacy, caution is recommended and additional contraceptives measures should be used.
149	Coadministration may increase drospirenone exposure. The clinical significance of this increase in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving substitution hormones in unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary. Clinical monitoring is recommended due to the potential risk for hyperkalaemia.
150	Coadministration may decrease comedication exposure. Monitor for signs of hormone deficiency.
151	Coadministration may increase comedication exposure. The clinical significance of this increase in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving substitution hormones in unknown. Postmenopausal women should be re-evaluated periodically to determine if treatment is still necessary.
152	Coadministration decreased ethinylestradiol exposure. An oral contraceptive should contain should contain at least 30 µg (European recommendation) or 35 µg (American recommendation) of ethinylestradiol if coadministered with atazanavir/ritonavir.
153	Coadministration decreased ethinylestradiol exposure. Alternative or additional contraceptive measures are recommended.
154	The effect of efavirenz on ethinylestradiol exposure varies according to the hormonal contraceptive method. No effect on ethinylestradiol exposure was seen with a combined oral contraceptive (COC) containing ethinylestradiol/norgestimate but exposure decreased with a vaginal ring releasing etonogestrel/ethinylestradiol (120/15 µg/day). With both methods, progestogen levels were markedly decreased and therefore use with efavirenz is not recommended as it may impair the contraceptive efficacy.

Table A2.2 Footnotes (continued)

Number	Interaction details
155	Coadministration increased etonogestrel exposure and decrease ethinylestradiol exposure. Since no dosage adjustment of ethinylestradiol is possible with the combined vaginal ring, alternative forms of contraception or barrier contraception in addition to the vaginal ring should be used.
156	Coadministration may increase etonogestrel exposure and decrease ethinylestradiol exposure. Since no dosage adjustment of ethinylestradiol is possible with the combined vaginal ring, alternative forms of contraception or barrier contraception in addition to the vaginal ring should be used.
157	Coadministration decrease levonorgestrel exposure. The Faculty of Sexual and Reproductive Healthcare Clinical Guidance states that the use of copper intrauterine device (Cu-IUD) is the most effective method for emergency contraception in women receiving an enzyme-inducing drug and that women who are not eligible for Cu-IUD should be offered a total of 3 mg levonorgestrel as a single dose for emergency contraception. This recommendation is supported by a pharmacokinetic study showing that levonorgestrel at a single dose of 3 mg was able to compensate the reduction in levonorgestrel Cmax and AUC due to efavirenz induction.
158	Coadministration decreased comedication exposure and, when used in a combined pill, the estrogen component was reduced. Given the lack of clinical data on the contraceptive efficacy, caution is recommended and additional contraceptives measures should be used.
159	A potential reduction of norethisterone contraceptive efficacy cannot be excluded in presence of efavirenz and an alternative contraceptive method or additional contraceptive measures should be used.
160	Coadministration may decrease comedication exposure and, when used in a combined pill, the estrogen component was reduced. Given the lack of clinical data on the contraceptive efficacy, caution is recommended and additional contraceptives measures should be used.
161	Coadministration may decrease ulipristal exposure and thus reduce the efficacy of the emergency contraception pill. Non-hormonal emergency contraception (i.e. a copper intrauterine device (Cu-IUD)) should be considered.
162	Coadministration may increase sildenafil exposure. Use sildenafil with caution at a reduced dose of 25 mg every 48 hours with increased monitoring for adverse events.
163	Coadministration increased sildenafil exposure. Use sildenafil with caution at a reduced dose of 25 mg every 48 hours with increased monitoring for adverse events.
164	Coadministration may decrease exposure of atazanavir. Atazanavir/ritonavir should be administered 2 hours before or 1 hour after antacids.
165	Coadministration may decrease rilpivirine exposure. Antacids should be administered at least 2 h before or 4 h after rilpivirine.
166	Bictegravir should be taken at least 2 hours before or 6 hours after antacids containing aluminium/magnesium. Simultaneously administration of bictegravir with antacids containing aluminium/magnesium is not recommended. Bictegravir can be taken under fasting conditions 2 hours before antacids containing aluminium, magnesium or calcium.
167	Simultaneous coadministration decreased dolutegravir exposure. Dolutegravir should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations, such as antacids. Medicinal products that reduce dolutegravir exposure (e.g. antacids) should be avoided in the presence of integrase class resistance.

Table A2.2 Footnotes (continued)

Number	Interaction details
168	Coadministration may decrease raltegravir exposure as divalent metal cations reduce raltegravir absorption by chelation. Coadministration with aluminium or magnesium antacids is not recommended. Coadministration of calcium carbonate antacids with once daily raltegravir is not recommended. If coadministration with an antacid is unavoidable, twice daily raltegravir can be administered with calcium carbonate antacids.
169	Coadministration may increase loperamide exposure, but this is unlikely to result in opioid CNS effects. Cardiac events including QT interval prolongation have been reported with high doses of loperamide. Caution is advised when loperamide is used at high doses for reducing stoma output, particularly as patients may be at increased risk of cardiac events due to electrolytes disturbances.
170	Coadministration may decrease atazanavir exposure. Refer to atazanavir product label for dosing recommendations, particularly with tenofovir, or in treatment naïve or experienced patient, or in pregnant patients.
171	Coadministration may decrease rilpivirine exposure. Only H2-receptor antagonists that can be dosed once daily should be used. Administer at least 12 h before or 4 h after rilpivirine.
172	Bictegravir may be subject to chelation by high concentrations of divalent cations which may result in reduced bictegravir concentrations. Bictegravir and calcium supplements can be coadministered simultaneously. The European product label for Biktarvy recommends they can be taken together without regard to food, but the US product label recommends to administer simultaneously with food. (The decision to administer with or without food should be decided on a case-by-case basis.)
173	Simultaneous coadministration decreased dolutegravir exposure. Dolutegravir should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations. The US Prescribing information suggests that, alternatively, dolutegravir and supplements containing iron or calcium can be taken together with food. Medicinal products that reduce dolutegravir exposure should be avoided in the presence of integrase class resistance.
174	Coadministration may decrease raltegravir exposure as divalent metal cations reduce raltegravir absorption by chelation. Coadministration with once daily raltegravir is not recommended and caution is recommended with twice daily raltegravir.
175	Bictegravir may be subject to chelation by high concentrations of divalent cations which may result in reduced bictegravir concentrations. It is recommended to administer bictegravir and mineral supplements containing iron or magnesium simultaneously with food.
176	Coadministration may decrease raltegravir exposure as divalent metal cations reduce raltegravir absorption by chelation. Coadministration with once daily raltegravir is not recommended. Administration of twice daily raltegravir should be separated by at least 4 hours.
177	Coadministration is not recommended as it may decrease exposure of the antiretroviral drug.
178	Simultaneous coadministration decreased dolutegravir exposure. Dolutegravir should be administered 2 hours before or 6 hours after taking medications containing divalent cations. Medicinal products that reduce dolutegravir exposure should be avoided in the presence of integrase class resistance.
179	Bictegravir may be subject to chelation by high concentrations of divalent cations which may result in reduced bictegravir concentrations. Divalent cations can be found in multivitamins. As the effect of cationic complexation cannot be excluded, it is recommended to administer bictegravir and multivitamins containing divalent cations simultaneously with food.

Table A2.2 Footnotes (continued)

Number	Interaction details
180	Coadministration may decrease raltegravir exposure as divalent metal cations reduce raltegravir absorption by chelation. Coadministration with once daily raltegravir is not recommended. Administration of twice daily raltegravir should be separated by at least 6 hours.
181	Coadministration could decrease cannabis exposure to a moderate extent.
182	Coadministration could potentially increase the effect of cannabis.
183	Coadministration may increase cocaine exposure. Ensure the patient is aware of signs/symptoms of toxicity. In addition, caution and close monitoring is recommended as both drugs have risks of QT prolongation.
184	Coadministration may increase comedication exposure. Ensure the patient is aware of signs/symptoms of toxicity.
185	Coadministration could potentially increase the serum level of the hepatotoxic cocaine metabolite
186	Coadministration could potentially reduce the effect of LSD.
187	Coadministration may increase methamphetamine exposure, although to a moderate extent. As dosing of recreational drugs can be variable, caution is advised.
188	Coadministration may increase ciclosporin exposure. More frequent therapeutic concentration monitoring is recommended until plasma levels have been stabilised.
189	Coadministration may decrease ciclosporin exposure. Close monitoring is recommended with appropriate dose adjustment of ciclosporin.
190	Coadministration is expected to substantially increase atorvastatin exposure and is not recommended. If coadministration is considered necessary, the lowest possible dose of atorvastatin should be used and the daily dose should not exceed 10 mg with careful safety monitoring.
191	Coadministration increased atorvastatin exposure. Start with atorvastatin 10 mg once daily with careful monitoring and increase dose if required based on the clinical response. A daily dose of 40 mg atorvastatin should not be exceeded. (Note, the US product label for darunavir/ritonavir states not to exceed atorvastatin 20 mg/day.)
192	Coadministration increased atorvastatin exposure and is not recommended. If coadministration is considered necessary, the lowest possible dose of atorvastatin should be used and the daily dose should not exceed 20 mg with careful safety monitoring.
193	Coadministration decreased statin exposure and decreased the exposure of total active drug. Monitor lipid values and adjust the statin dose based on the clinical response.
194	Coadministration may increase pravastatin exposure. It is recommended to start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety.
195	Coadministration increased pravastatin exposure. It is recommended to start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety.
196	Coadministration may decrease statin exposure. Monitor lipid values and adjust statin dose based on clinical response.
197	Coadministration may increase colchicine exposure. Refer to the product label for dose recommendations for the treatment/prophylaxis of gout flares and the treatment of familial Mediterranean fever. Coadministration is contraindicated in patients with renal or hepatic impairment.

Table A2.2 Footnotes (continued)

Number	Interaction details
198	Enhanced levodopa effects including severe dyskinesia have been reported with some protease inhibitors. Monitor for levodopa/carbidopa efficacy.
199	Coadministration may increase dexamethasone concentrations and a dose adjustment may be required. Careful monitoring for steroid-related adverse effects is recommended. Chronic or high doses of dexamethasone may also decrease exposure of the antiretroviral drug with the possible loss of therapeutic effect and development of resistance. Use with caution.
200	Coadministration may decrease dexamethasone concentrations and a doubling of dexamethasone dose would be recommended when used in COVID-19 treatment.
201	Coadministration may increase comedication concentrations and a dose adjustment may be required. Careful monitoring for steroid-related adverse effects is recommended.
202	Coadministration increased comedication concentrations and a dose adjustment may be required. Careful monitoring for steroid-related adverse effects is recommended.

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