World Health Organization

GUIDELINES

UPDATED RECOMMENDATIONS ON

HIV PREVENTION, INFANT DIAGNOSIS, ANTIRETROVIRAL INITIATION AND MONITORING

MARCH 2021

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Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring: March 2021

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CONTENTS

Index of tables, figures and boxes

Web annexes

I. ABBREVIATIONS AND ACRONYMS

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral (drug)
CI	confidence interval
COVID-19	coronavirus disease
DALY	disability-adjusted life-year
DTG	dolutegravir
EFV	efavirenz
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIV	human immunodeficiency virus
NNRTI	non-nucleoside reverse-transcriptase inhibitor
PI	protease inhibitor
PICO	population, intervention, comparison and outcome
PrEP	pre-exposure prophylaxis
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS

II. DEFINITION OF KEY TERMS

General

HIV refers to the human immunodeficiency virus. There are two types of HIV: **HIV-1 and HIV-2.**

HIV-1 is responsible for the vast majority of HIV infections globally.

Acute (HIV) infection is the period between a person being infected with HIV and HIV antibodies being detectable by a serological assay.

Age groups and populations

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.

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, 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.

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. Each country should define the specific populations that are vulnerable and key to their epidemic and response, based on the epidemiological and social context.

Substantial risk of HIV infection is provisionally defined as an incidence of HIV greater than 3 per 100 person-years in the absence of pre-exposure prophylaxis (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.

HIV testing and 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.

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, and serological assays can be used for children older than 18 months of age.

Point-of-care testing is conducted at the site at which clinical care is being provided, with results being returned to the patient or caregiver on the same day as sample collection and test to allow for clinical decisions to be made in a timely manner.

PrEP (pre-exposure prophylaxis) of HIV is the use of ARV drugs by people who are not infected with HIV to prevent the acquisition of HIV.

Antiretroviral therapy

ARV (antiretroviral) drugs refer to the medicines used to treat HIV.

ART (antiretroviral therapy) refers to the use of a combination of three or more ARV drugs for treating HIV infection.

Use of ARV drugs for HIV prevention refers to the HIV prevention benefits of ARVs and includes those used for preventing the mother-to-child transmission of HIV, to reduce the transmission of HIV to serodiscordant sexual partners[1] and to prevent the acquisition of HIV when a person is exposed (post-exposure prophylaxis and PrEP).

Viral suppression is a viral load that is undetectable, equal to or less than 50 copies/ml.

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.

Virological failure refers to the inability of a treatment plan to achieve or maintain viral suppression below a certain threshold. Virological failure is defined by a persistently detectable viral load exceeding 1000 copies/ml after at least six months of using ART.

Service delivery

Adherence is the extent to which a person's behaviour – for instance taking medication, following a diet and/or changing lifestyle – corresponds with agreed recommendations from a health-care provider.

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.).

A **public health approach** addresses the health needs of a population or the collective health status of people rather than focusing primarily on managing individual cases. This approach aims to ensure the widest possible access to high-quality services and medicines 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.

[1] Serodiscordant couples are couples in which one partner is living with HIV and the other is HIV-negative. A couple refers to two people in an ongoing sexual relationship; each of these people is referred to as a partner in the relationship. How individuals define their relationships will vary according to their cultural and social context.

III. ACKNOWLEDGEMENTS

WHO gratefully acknowledges the contributions of many individuals and organizations to the development of this guideline.

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V. EXECUTIVE SUMMARY

Audience

The primary audience for this guideline is national HIV programme managers, people living with HIV, health-care providers and policy-makers in low- and middle-income countries. This guideline update will be a useful resource for clinicians and should help to shape the priorities of policy-makers in development agencies, international organizations, nongovernmental organizations and other implementing partners. This guideline will also be of value to people living with HIV, communities and civil society organizations to ensure they are informed of the updated guidance and to help suport their implementation activities in-country.

Process of guideline development

This guideline update was developed in accordance with procedures established by the WHO Guidelines Review Committee. The recommendations in the guidelines are based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to reviewing evidence and formulating recommendations.

Background and rationale

WHO promotes a public health approach to scale up testing, prevention, treatment and care to people living with HIV in resource-limited settings. This approach aims to meet targets set out in the Sustainable Development Goals, including the promise made by Member States to end AIDS as a public health threat by 2030.

In 2016, WHO updated the consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection and the consolidated guidelines on HIV prevention, diagnosis, treatment and care of key populations, issuing important recommendations across the HIV care continuum. This included guidance on the prevention of HIV using oral pre-exposure prophylaxis (PrEP) and uptake of antiretroviral therapy (ART) in national programmes, including the WHO "treat all" policy (treatment for all people living with HIV regardless of CD4 cell count or clinical symptoms). The 2016 recommendations also included guidance on monitoring the treatment of people living with HIV and the timing of ART among those initiating treatment of several opportunistic infections. The 2016 update was followed by recommendations for rapid ART initiation and management of advanced HIV disease in 2017 and the introduction of dolutegravir (DTG) as the preferred option in first-line regimens in 2018 and in second-line regimens (if not previously used in first-line) in mid-2019. Updated recommendations on infant diagnosis and HIV testing strategies were released in 2018 and 2019, respectively. The recommendations developed for this guideline, and other relevant guidelines developed since 2016, will be integrated with the updated consolidated HIV guidelines that will be released in the second half of 2021.

In response to emerging evidence, experience and practice in countries and a scoping of key clinical areas to be updated within the consolidated HIV guidelines, this publication provides new or updated recommendations and implementation considerations on the following clinical topics: (1) introduction of the dapivirine vaginal ring as a new prevention option for women with substantial risk of HIV infection; (2) the use of point-of-care technologies for both infant diagnosis and treatment monitoring; and (3) earlier initiation of ART among people with HIV and tuberculosis. These recommendations (Table) intend to optimize HIV treatment monitoring, provide more options for HIV combination prevention and further harmonize ART for those initiating treatment for tuberculosis among coinfected individuals and for people being evaluated for rapid ART initiation, including same-day start. The implementation of these recommendations within the overall public health approach will support further reductions in HIV incidence and HIV-associated illness and death.

WHO would like to acknowledge and thank the numerous contributors to these guidelines that were developed during the COVID-19 pandemic and WHO remains committed to engage with the global HIV community and Member States to ensure the continuity and quality of care for people living with HIV during and beyond the COVID-19 pandemic.

Summary of new recommendations

The following table summarizes all the new and updated recommendations included in these guidelines, including the strength of the recommendation and certainty of the evidence. For ease of navigation, this table also includes the sections for the revised treatment monitoring algorithm and updated clinical considerations for rapid ART initiation. Clicking the hyperlink will take you straight to that section.

Table. Summary of new and updated recommendations and key guidance

Recommendations and key guidance updates	Update or new	Link to section
2. CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION		
The dapivirine vaginal ring may be offered as an additional prevention choice for women at substantial risk[a] of HIV infection as part of combination prevention approaches *(Conditional recommendation; moderate-certainty evidence)* *[a] Substantial risk of HIV infection is defined as HIV incidence greater than 3 per 100 person-years in the absence of PrEP.*	New	Section 2.1
3. CLINICAL GUIDELINES: DIAGNOSTICS AND TREATMENT MONITORING		
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)*	Updated[2]	Section 3.1
Point-of-care viral load may be used to monitor treatment among people living with HIV receiving ART *(Conditional recommendation; moderate-certainty evidence)*	New	Section 3.2
Revised treatment monitoring algorithm	Updated[3]	Section 3.3
4. CLINICAL GUIDELINES: TIMING OF ANTIRETROVIRAL THERAPY		
ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 count, among people living with HIV[b] Adults and adolescents *(Strong recommendation, low- to moderate-certainty evidence)* Children and infants *(Strong recommendation, very-low-certainty evidence).* *[b] Except when signs and symptoms of meningitis are present.*	Updated[4]	Section 4.1
Revised TB and HIV clinical considerations for rapid ART initiation	Updated[5]	Section 4.2

[2] Updated from a conditional recommendation made in 2016 that was based on low-certainty evidence.

[3] The treatment monitoring algorithm was revised based on additional data available since 2016 and new optimized treatment options recommended by WHO.

[4] The recommendation reduced the time required for ART initiation from after eight weeks to within two weeks. The previous strength of recommendation was strong, with high-quality evidence, but did not include people living with HIV with profound immunosuppression.

[5] The earlier clinical consideration was informed by expert opinion that a brief delay in ART initiation might be beneficial – on reviewing evidence from the systematic review and prevailing practices in countries, the Guideline Development Group agreed that initiating ART was a priority and that TB symptoms may be evaluated simultaneously while initiating ART rapidly.

1. INTRODUCTION

1.1 Background and rationale

HIV infection is a public health issue. In 2019, more than 38.0 million [31.6 million–44.6 million] people were living with HIV, and more than 1.7 million [1.2 million–2.2 million] people acquired HIV. Nearly 61% of the people newly infected with HIV live in sub-Saharan Africa. Between 2010 and 2019, the epidemic also continued to grow in eastern Europe and central Asia, with the number of people acquiring HIV rising by 72%. There were also increases in the Middle East and North Africa (22%) and Latin America (21%) *(1)*. The United Nations General Assembly agreed in June 2016 that ending AIDS as a public health threat by 2030 requires a Fast-Track response, with three milestones to be reached by 2020 *(2)*. These milestones include reducing the number of people newly infected with HIV to fewer than 500 000 per year globally, reducing the number of people dying from AIDS-related causes to fewer than 500 000 per year globally and eliminating HIV-related stigma and discrimination *(3)*. Although the number of people dying from AIDS-related causes has steadily declined by nearly one third and annual incidence is the lowest since 1989, these global targets have not been achieved and remain a significant challenge.

These guidelines provide updated and new recommendations on prevention, infant diagnosis, treatment monitoring and antiretroviral therapy (ART) among those initiating treatment for tuberculosis (TB). The recommendations developed for this guideline will be integrated with the updated consolidated HIV guidelines that will be released in the second half of 2021. The following paragraphs outline the rationale for including these topics in the guidelines.

Prevention

Providing and scaling up ART alone is not sufficient to end the HIV epidemic. A comprehensive approach is needed that includes combination HIV prevention, which will help to further reduce the number of people newly infected *(4)*. For this to succeed, social, cultural and structural factors need to be addressed that put people at risk and undermine access to services. Adolescent girls and young women are still disproportionately affected by HIV and subject to many forms of discrimination across the globe. In 2017, 79% of the adolescents 10 to 19 years old newly infected with HIV in eastern and southern Africa were female *(5)*. Ensuring that young people have the skills, knowledge and capacity to protect themselves against HIV and have access to comprehensive sexual and reproductive health services is an important component of achieving prevention goals.

WHO currently recommends that oral pre-exposure prophylaxis (PrEP), containing tenofovir disoproxil fumarate (TDF), should be offered as an additional prevention choice for people at substantial risk of HIV infection *(6)*. The promising results of the dapivirine vaginal ring, a novel prevention intervention, were viewed as a potential additional choice for women at substantial risk of HIV that may better suit their prevention preferences and needs and was thus included for review in these guidelines. Other novel biomedical prevention methods are on the horizon such as long-acting injectable cabotegravir. However, data were not yet available for the Guideline Development Group to consider.

Infant diagnosis

In 2019, an estimated 1.63 million infants were tested globally in low- and middle-income countries, an increase from 1.59 million tests in 2018 *(7)*. This translates into an estimated coverage of about 60% according to some estimates *(1)* but does not reveal the full picture. Morbidity and mortality among infants remains unacceptably high, with more than 160 000 infants acquiring HIV and more than 100 000 dying from AIDS-related causes reported *(7)*. Significant efforts have been made to scale up infant diagnosis and optimize treatment regimens for infants and children, but significant gaps in access to testing and uptake remain. The challenges of often-centralized laboratory-based infant diagnosis and complicated treatment options result in only about half of infants and children living with HIV being linked to and initiated on ART. Access to early infant diagnosis has remained relatively stagnant, with only 50% of exposed infants receiving an HIV test within the first two months of life *(1)* and significant differences observed across countries. Cheaper, faster and more accurate testing strategies and technologies are therefore needed to help reduce the number of cases missed, increase opportunities for prevention and provide rapid access to life-saving ART.

Treatment monitoring

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. Viral load testing has been the preferred approach to treatment monitoring since 2016, along with a treatment monitoring algorithm to identify treatment failure, provide timely adherence interventions and identify the possibility of drug resistance, which may necessitate transitioning individuals to a second-line ART regimen. There has been significant uptake of viral load testing since 2016, with approximately 20 million viral load tests being conducted across low- and middle-income countries in 2020 *(7)*. Despite these increases, challenges persist. Access to viral load testing needs to expand to all people living with HIV, and since testing results are not always consistently used for clinical decision-making, the treatment monitoring algorithm required revision given better optimized drug regimens *(8,9)*.

Recent evidence has suggested that point-of-care viral load technologies could improve test turnaround times, viral suppression rates and retention in care. The use of point-of-care viral load testing could promote the use of viral load in a variety of settings, such as in specific populations critically needing a faster test and result. For example, it could be used for pregnant and breastfeeding women to prevent transmission, people with advanced HIV disease, infants and children and people suspected of having drug resistance.

In addition, with newer and more robust antiretroviral (ARV) regimens being introduced in 2019, this guideline process included a critical review of the previous treatment monitoring algorithm to ensure optimal patient care in the context of new evidence and tools that have become available since 2016.

People living with HIV coinfected with TB

TB remains the leading cause of death among people living with HIV. In 2019, TB accounted for 1.2 million (range, 1.1 million–1.3 million) deaths. Among these, 8.2% were people living with HIV *(10)*. In 2019, an estimated 10.0 million (range, 8.9 million–11.0 million) people developed TB worldwide, of which 8.2% were people living with HIV. Even when receiving ART, people living with HIV are three times more likely to die during TB treatment and continue to suffer disproportionately from this preventable and curable disease. ART has been proven to reduce TB incidence and mortality; however, although global ART coverage is estimated to be 59%, only 41% of the people living with HIV estimated to have TB are receiving ART *(10)*.

Currently, WHO recommends rapid ART initiation (within one week and the same day if ready) for all people diagnosed with HIV, unless there are clinical indications to delay treatment. These include the recommendation to initiate TB treatment first, followed by ART as soon as possible within the first two months of TB treatment for those diagnosed with both TB and HIV. Another clinical consideration for rapid ART initiation is to briefly delay ART while investigating for TB among people with TB symptoms. There is a need to assess whether initiating ART earlier would help to further reduce unnecessary morbidity and mortality while addressing concerns of potentially increased incidence of immune reconstitution inflammatory syndrome.

1.2 Objectives

These guidelines are intended to contribute to the 13th WHO Global Programme of Work – Triple-Billion initiative – as part of the Global Public Health Goods 1.1.2 as well as the objective to meet targets set out in the Sustainable Development Goal 3 to end of AIDS by 2030.

1.3 Target audience

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

- national HIV treatment and prevention advisory boards;
- national TB and HIV programme managers;
- managers of maternal, newborn and child health programmes;
- managers of sexual and reproductive health programmes;
- clinicians and other health service providers;
- managers of national laboratory services;
- people living with HIV and key population networks and organizations
- community-led and community-based organizations and service providers; 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 guidelines should contribute to and expedite the achievement of key global and national HIV goals for 2016–2021 *(11)*, contribute to the new Global Programme of Work – Triple-Billion initiative – as part of the Global Public Health Goods 1.1.2 and to realizing the Sustainable Development Goals *(12)*.
- The guidelines are based on a public health approach to scaling up the use of ARV drugs along the continuum of HIV prevention, treatment and care.

- The development and implementation of the guidelines should realize the rights and responsibilities of people living with HIV and promote the principles of the greater involvement of people living with HIV and meaningful involvement of people living with HIV.
- In addition to strengthening the continuum of high-quality HIV services, the recommendations in the guidelines should be implemented with a view to strengthening broader health systems, especially primary and chronic care.
- Implementation of the guidelines needs to be accompanied by efforts to promote and protect the human rights of people who need HIV services, including ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity and equity for people living with disabilities.
- Implementation of the recommendations in these guidelines should be informed by local context, including HIV epidemiology, availability of resources and comorbidities, the organization and capacity of the health system and anticipated cost–effectiveness.

1.5 Methods for developing the guidelines

This publication is linked to the 2016 WHO consolidated guidelines *(4)* and to previous guidelines developed in 2017, 2018 and 2019. These are collectively being compiled into a single consolidated publication containing all relevant guidance.

Annex 1 details the full methods for developing this guideline. In summary, this guideline update was developed in accordance with procedures established by the WHO Guidelines Review Committee *(13)*. The recommendations in the guidelines are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to reviewing evidence and formulating recommendations *(14)*. Consistent with previous WHO guidelines, this guideline is based on a public health approach that considers feasibility and effectiveness across a variety of settings.

All external contributors to the guidelines, including members of the Guideline Development Group and the External Review Group, completed a WHO declaration of interests form in accordance with WHO policy for experts. The WHO Guideline Steering Group reviewed the declaration of interest forms and the results of the web-based search for each member of the Guideline Development Group, and a management plan was agreed and recorded for each individual and presented at the guidelines meeting.

The systematic reviews[6] and evidence-to-decision-making tables (see Web Annexes) prepared in accordance with the GRADE process, were shared in advance and presented at the meetings, and the methodologist facilitated discussions. The recommendations were formulated by the Guideline Development Group who met virtually via Zoom teleconferencing from 28 September to 2 October 2020. The draft guidelines were circulated for review to members of the Guideline Development Group and the External Review Group in November 2020.

[6] All supporting evidence that informed this guideline's development is available in the Web Annexes

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2. CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

2.1 The dapivirine vaginal ring

Recommendation

The dapivirine vaginal ring may be offered as an additional prevention choice for women at substantial risk[a] of HIV infection as part of combination prevention approaches.

(conditional recommendation; moderate-certainty evidence)

[a] Substantial risk of HIV infection is defined as HIV incidence greater than 3 per 100 person–years in the absence of PrEP (see Box 1).

Background

PrEP (pre-exposure prophylaxis) is the use of ARV drugs by HIV-negative individuals to reduce the acquisition of HIV infection. The results from randomized trials and subsequent open-label extension studies and demonstration projects found oral PrEP containing tenofovir to be protective against HIV infection across populations *(1)*. As a result, WHO recommended daily oral PrEP containing tenofovir as an additional prevention choice for people at substantial risk of HIV infection in 2015 *(2)*. Since WHO released the recommendation on oral PrEP, more than 57 low- and middle-income countries have incorporated PrEP into their national HIV guidelines, and PrEP is provided in 34 low- and middle-income countries *(3)*.

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 female-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 28 days and then should be replaced by a new ring *(4)*.

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 *(5)* 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 services they are already comfortable attending, especially services for contraception and for sexually transmitted infections *(6)*.

Initial outcomes from oral PrEP programmes for women are mixed *(7)*. Some programmes report low uptake and low continuation. 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 *(8)*. 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 *(8,9)*.

Other novel biomedical prevention methods are on the horizon, such as long-acting injectable cabotegravir. Although this is an exciting development in HIV prevention, data were not yet available for the Guideline Development Group to consider. However, there are plans to consider this in the near future.

Box 1. Defining "substantial risk"

Substantial risk of HIV infection is provisionally defined 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. Individual risk varies within groups at substantial risk depending on individual behaviour and the characteristics of sexual partners. Most of the PrEP trials reviewed for the 2015 WHO recommendation identified and recruited groups at substantial risk of acquiring HIV, as demonstrated by the HIV incidence rate among participants in control arms that ranged between 3 and 9 per 100 person-years in most studies. In locations where the overall incidence of HIV infection is low, there may also be individuals at substantial risk who would desire and benefit from PrEP services *(2)*.

HIV incidence greater than 2 per 100 person-years was considered sufficient to warrant offering oral PrEP in the recommendations issued by the International Antiviral Society – USA expert panel in 2014 *(10)*. Thresholds for offering PrEP may vary depending on a variety of considerations, including epidemiological context or trends, available resources and the relative costs, feasibility and demand.

Risk assessment tools for better defining substantial risk were developed as part of the WHO PrEP implementation Tool *(11)*. WHO is considering simplifying these tools for broader use.

Rationale and supporting evidence

Summary of review findings

A systematic review and meta-analysis of dapivirine vaginal ring trials demonstrated that the it is effective in reducing the risk of acquiring HIV infection. Two randomized controlled trials – the Ring Study (IPM-027) *(12)* and ASPIRE (MTN-020) *(13)* reported that the dapivirine vaginal ring was approximately 30% effective in reducing HIV infection in intention-to-treat analysis. 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 *(14,15)*. The results from one of the open-label extension studies indicated a 62% reduction in HIV transmission, comparing study results to a simulated control *(14)*. The subgroup analysis by age did not show efficacy among women 18–24 years old, who had low adherence. Further studies are underway or planned to help understand whether this lack of effect 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 *(16)*. Safety and acceptability are also being studied among women 15–18 years old, who were not included in the trials. The dapivirine acts locally, and systemic absorption is low *(17)*. 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 *(18,19)*.

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 dapivirine vaginal ring to placebo arms (95% CI: 9–42%) *(20)*. Individually, ASPIRE found a 27% relative reduction in HIV risk (95% CI: 1–46%) *(21)*, and the Ring Study found a 33% relative reduction in HIV risk (95% CI: 5–53%) *(22)* 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%) *(21)*. 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 dapivirine vaginal ring versus placebo among women 25 years and older (95% CI: 32–77%) *(21)*. A post hoc analysis showed lower adherence and no efficacy 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 *(12)*. 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 in participants 21 years or younger *(20)*.

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 *(14,15)*. The results from DREAM indicated a 62% reduction in HIV risk compared to 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 *(15)*.

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 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 (relative risk (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 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) *(23)*.

ASPIRE reported on study-related social harm, defining them as "nonmedical adverse consequences of dapivirine vaginal ring use or of trial participation more generally" *(24)*. 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 a social harm was associated with short-term decreased product adherence *(24)*.

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 III randomized controlled trials show no increased risk for NNRTI-resistant HIV infection for dapivirine vaginal ring compared to placebo arms (RR = 1.13, 95% CI: 0.64–2.01; low-certainty evidence) *(23)*.

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 dapivirine vaginal ring compared to placebo arms (moderate-certainty evidence) *(25)*. 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 dapivirine vaginal ring compared to placebo arms (very-low-certainty evidence) *(26,27)*. 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 *(28)*. 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 *(28)*.

Cost and cost–effectiveness

According to the International Partnership for Microbicides, the current cost to procure the ring alone is US$ 8 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 overall cost of providing the dapivirine vaginal ring is expected to cost less than providing oral PrEP since, from a provider perspective, it requires fewer health system resources. For example, the only associated laboratory cost is HIV testing. One study from South Africa found that the dapivirine vaginal ring would be a cost-saving intervention for KwaZulu-Natal if the intervention was provided as a priority for female sex workers *(29,30)*. 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 risk groups was achieved *(31)*. 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 *(32,33)*.

Feasibility

Multiple studies of the dapivirine vaginal ring have been conducted in countries in southern and eastern Africa, thus proving its feasibility across settings where the ring is intended to be implemented. In addition to the safety study, two Phase III 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 *(34–36)*. 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 and Zimbabwe) have already begun to develop plans 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 *(37)*. Most women disclosed ring use to their male partners, although some women

feared violence or anger from partners if ring use was discovered *(38)*. 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 *(37)*.

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 *(37)*. 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 *(38)*.

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 *(39)*. 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 *(40)*. The results from safety studies among postmenopausal women and adolescents in the United States of America also found the ring highly acceptable *(36,41)*. 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 *(42)*. 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 *(40, 43–47)*.

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 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 (i.e., increased options may lead to increased use) *(48)*. 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.

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 provision or referral to services that prevent and protect against gender-based violence. Where feasible, providing voluntary partner services should also be considered *(49)*. 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.

Delivery sites

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 sites best suited to offer the dapivirine vaginal ring.

Adherence support

Similar to oral daily PrEP, the dapivirine vaginal ring needs to be used continuously as prescribed 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 reproductive-aged women. 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 *(50)*.

In the ASPIRE trial, 169 of the 2629 women enrolled became pregnant during the trial *(26)*. 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 *(18,19)*. 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 registrar 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) *(51)*) to assess feasibility and effectiveness 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 dapivirine vaginal ring with key population groups, especially 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. The use of dapivirine vaginal ring in combination with other prevention interventions and intermittent use of 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.

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3. CLINICAL GUIDELINES: DIAGNOSTICS AND TREATMENT MONITORING

3.1 Point-of-care infant diagnosis

Recommendation

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)

Background

Although significant recent investments in improving the diagnostic networks, centralized laboratories and sample collection networks have been made in most high-burden settings, 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 nucleic acid test within the first two months of age *(1)*. 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 *(2,3)*. 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 44.5 days *(4)*. The time between the results received at the clinic to receipt by the caregiver was 43.7 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 infants living with HIV had died between infant testing and ART initiation.

HIV nucleic acid tests 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 *(5)*. 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 *(6)*. 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 have been considered to potentially update the 2016 recommendation.

Rationale and supporting evidence

Summary of review findings

A systematic review *(7)* of the clinical impact of using same-day point-of-care infant diagnosis compared to laboratory-based technologies identified seven studies *(8–14)* of more than 37 000 infants across 15 countries in sub-Saharan Africa. 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 homogeneous and consistent across studies. Most studies had a low risk of bias for critical outcomes (including 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) 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 (95% CI: 35–37) and ranged from 8 days to 125 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 *(8–12,14)*. 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 standard of care, the median time from sample collection to treatment initiation was 39.5 days (95% CI: 34–43) and ranged from 6 days to 127 days. The evidence was of high certainty overall.

Proportion of infants living with HIV initiated on 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 compared to 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 initiation of treatment *(10,11)*. 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 RR: 1.40) *(10)*. The second study, from Zambia, found high mortality rates in both arms but no 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 *(11)*. Overall, there was very-low-certainty evidence for these outcomes.

The systematic review had several limitations. First, all studies were from sub-Saharan Africa. However, 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 review and synthesis of available cost–effectiveness models was developed using four cost–effectiveness studies and two overarching modelling approaches *(15):* Johns Hopkins' model focusing on sub-Saharan Africa and Zambia *(16,17);* and the Cost–effectiveness of Preventing AIDS Complications (CEPAC)-Paediatric model in Zimbabwe *(18,19).* 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 person 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 to the standard of care. In Zambia, point-of-care testing cost US$ 752 less than the standard of care per additional ART initiation when sharing the devices 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.

Currently, in four countries with a high burden of HIV (Malawi, Mozambique, Uganda and Zambia), access to same-day point-of-care testing is estimated to already be 30–50% currently. 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.[7] 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 (initiation rates based on the above systematic review). 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 ART initiation.

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 as well as elders, data were collected before point-of-care testing was introduced and after it had been in use for at least three months *(20).* Reduced time to receive test results lowered caregiver anxiety about the child's HIV status and allowed families to start treatment earlier. Some considered printed point-of-care results as more trustworthy than conventional handwritten results, believing

[7] Clinton Health Access Initiative. Point-of-care infant diagnosis affordability analysis across four sub-Saharan African countries. 2020.

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.[8] 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% saw 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 of structured interviews with health-care workers providing infant testing services and semi structured interviews with national and regional laboratory managers or early infant diagnosis programme managers – before and after point-of-care infant testing was implemented *(21)*. 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 of 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.

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.

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 *(22).*

[8] WHO survey on values and preferences to inform these guidelines. See the methods in Annex 1 and the web annexes for more information.

Feasibility

Several technologies are on the market and available for use at the point of care; two already have WHO prequalification (5). Many such devices have already been procured and are in use 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. Across 140 high-burden developing countries (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 of 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.[9] 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 *(23).* 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 decision

The Guideline Development Group formulated a strong recommendation favouring point-of-care nucleic acid testing 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.

[9] Clinton Health Access Initiative. Point-of-care infant diagnosis affordability analysis across four sub-Saharan African countries. 2020.

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 a nucleic-acid test is required *(24)* (Annex 2).

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 (TB, HIV viral load, etc.).

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.

3.2 Point-of-care viral load testing

Recommendation

Point-of-care viral load may be used to monitor treatment among people living with HIV receiving ART.

(conditional recommendation; moderate-certainty evidence)

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 treatment regimen *(6)*. 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 *(25)*. 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 test turnaround times and clinical utilization of 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 now listed for procurement by Member States *(26)*.

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 critical 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 comparing point-of-care viral load testing with laboratory-based testing identified 35 studies for inclusion – seven included relevant clinical impact data: one randomized controlled trial (STREAM study) and six observational studies. However, only three studies (one randomized controlled trial and two observational studies) compared point-of-care testing directly with the standard of care *(27–30)*. 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, when 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) *(28)*. Using 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)] (28). 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 viral suppression and retention in care

Only the randomized controlled trial included long-term viral suppression and/or retention in care outcomes *(28)*. Of everyone who received a point-of-care test, 90% were retained in care and achieved viral suppression (<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 patients with sustained viral suppression

Only the randomized controlled trial included the transfer to differentiated care outcome for people with sustained viral suppression *(28)*. 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.

Limitations

Only one randomized controlled trial and two observational studies were available for inclusion that compared point-of-care testing with standard-of-care testing and included key outcomes. Both studies were conducted in Africa. Five additional randomized clinical trials remain ongoing. In addition, the need and importance of giving priority to high-risk groups were lacking.

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 *(31–33)*. Overall, point-of-care testing across the three studies was found to be cost-effective compared with standard of care even when accounting for local context and different implementation approaches, accounting for local context and implementation approaches. These studies did not include potential cost savings to patients associated with fewer facility visits.

Values and preferences

An online survey carried out by WHO to inform these guidelines (see Annex 1) was provided to 43 people living with HIV to understand their values and preferences for point-of-care viral load testing versus laboratory-based testing. The majority (81%) of people living with HIV thought it would be acceptable to monitor their treatment using same-day testing, 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%).

Acceptability and feasibility

In addition, an online survey[10] 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.

Survey of 51 health-care workers

The majority (91%) of health-care workers thought 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 conduct 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.

Survey of 43 programme managers

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 was recently published incorporating an individual patient data meta-analysis for the Cepheid GeneXpert® – included 14 data sets from 13 eligible studies *(41)*. 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 publications have provided accuracy data on the Abbott m-PIMA™ device *(35,43)*. 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 *(43)*.

[10] WHO survey on values and preferences to inform 2020 clinical guidelines. WHO 2020. [Web annex]

Feasibility

Technologies are on the market and available for use at the point of care. Two already have WHO prequalification *(26)*; 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 *(44)*), 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 *(44)*. This leaves available capacity for expanding TB testing and considering HIV infant and viral load testing. However, conducting 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 patients should therefore be considered.

Equity

Ethical and equity considerations were summarized to guide the discussions during the guideline meeting *(23)*. Given the likely benefits associated with point-of-care for viral load testing, all efforts should be undertaken to make them 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 include, 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, like 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 do 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 for decision

The Guideline Development Group formulated a conditional recommendation favouring point-of-care viral load testing to monitor the treatment in 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 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 viral suppression, retention in care and transfer to differentiated care for those with sustained viral suppression; 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

Several implementation considerations were highlighted.

First, point-of-care viral load technologies should be considered and used within the current treatment monitoring algorithm (Fig 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 patients should therefore be considered. A targeted testing or triaging approach may therefore be necessary (see Box 2). 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 2. Priorities for point-of-care viral load testing

Point-of-care viral load testing should be given priority for the following populations:

- 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 patient health. Maximizing the clinical impact of point-of-care testing and reduce 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

Several research gaps were identified. 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 of 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 well as 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.

3.3 Treatment monitoring algorithm

Background

Viral load testing was strongly recommended as the preferred approach to monitor treatment among people living with HIV in 2016, with the associated development of a treatment monitoring algorithm to try to identify those who need to switch to second-line treatment if drug resistance is suspected *(6)*.

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 (often on the same day as the diagnosis of HIV) and transition from first-line ART regimens containing NNRTIs, primarily efavirenz (EFV) to DTG, an integrase inhibitor that has so far exhibited a very high barrier for drug resistance *(20,45)*. In addition, pretreatment drug resistance to NNRTI-based regimens has increased over the years *(46)*.

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;
- immediate (single viral load test) switch of therapy for those receiving NNRTI-based regimens; and
- treatment failure threshold.

Rationale and supporting evidence

Timing of the first viral load

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 ART initiation 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 *(47)* of non-pregnant adults including six studies *(48–53)*, after one month on ART, 70% receiving DTG-based regimens had suppressed viral loads at <50 copies/ml versus only 20% on EFV-based regimens. After three months, 87% receiving DTG-based regimens and 63% receiving EFV-based regimens had suppressed viral loads. By six months on ART, there were few differences in overall suppression to <50 copies/ml between regimens. For children, data from randomized trials and observational studies suggest that infants and children may take longer than in 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 after initiating ART with NNRTI-based therapy versus 94% by six months (54). 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 *(55)*.

Early suppression of viral loads was significantly decreased among people with baseline viral loads >100 000 copies/ml, with low rates of suppression of viral loads at month one even among people receiving DTG-based regimens *(47)*. Similarly, children with viral loads greater than 100 000 copies/ml had poor suppression rates one and three months after initiating ART.

Detecting earlier treatment failure resulting from pretreatment drug resistance would be beneficial, especially for individuals starting NNRTI-based regimens. However, balancing this with potential overestimation of treatment failure if viral load testing is done 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 that the first viral load result be more urgently available and reviewed by six months after initiating ART.**

Timing of repeat viral load test after 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. Limited evidence was available to support the review of this question; however, the literature noted some key considerations. First, the three- to six-month period indicated in the 2016 algorithm was considered to lack clarity so that the timing of the repeat viral load test was inconsistently implemented. Second, all related studies highlighted substantial delays in conducting repeat testing *(47)*. 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 compliance 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 subsection 3.2).

Immediate (single viral load test) switch of therapy for those receiving NNRTI-based regimens

This element was only considered for NNRTI-based regimens and not for DTG- or protease inhibitor (PI)-based regimens. Key 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, and the prevalence of acquired resistance to NNRTIs ranged from 71% in Nicaragua to 92% in Senegal 48 months or later after initiating ART *(46)*. However, the confidence intervals for these data were wide. Two articles reviewed drug resistance levels among adults living with HIV on TDF + lamivudine or emtricitabine (FTC) + EFV regimens in several low- and middle-income countries *(56,57)*. In treatment cohorts from 1998 to 2015 of adults receiving regimens containing TDF, lamivudine or emtricitabine and EFV or nevirapine, the prevalence of NNRTI mutations at failure ranged from 42% in eastern Africa to 82% in western and central Africa (56). Southern Africa had a mid-range of 59% NNRTI resistance *(57)*. Further, children and adolescents receiving NNRTI-based regimens have high levels of drug resistance *(46)*.

A recent systematic review and meta-analysis *(58)* found that 46% of the people receiving NNRTI-based first-line ART resuppressed at the next viral load, 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 their goal of viral suppression *(63)*.

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) may have health benefits and reduce HIV transmission and mortality, especially for those with drug resistance *(64,65)*. This intervention is cost-effective based on a cost–effectiveness threshold of US$ 500 per DALY averted, even though some people living with HIV would be unnecessarily switched to second-line therapy.

In summary, available data suggest that a large proportion (40–97%) of the people in low- and middle-income countries receiving NNRTI-based ART regimens with a single elevated viral load result have drug resistance and would benefit from immediately switching to second-line ART. Further, despite WHO recommendations, completion of the viral load cascade (adherence counselling and repeat viral load testing) for those with a first elevated viral load result is low – available evidence suggesting that fewer than 25% receive the repeat viral load test *(40,66)*. Switching therapy 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, especially for pregnant and breastfeeding women. However, in some countries, 30–40% of the people receiving NNRTI-based regimens with elevated viral load do not have drug resistance and thus would be unnecessarily switched to second-line ART.

An immediate switch algorithm could identify treatment failure more quickly; however, clinical support would be necessary to ensure more rapid switching to second-line ART. Emphasizing adherence and strengthening adherence counselling during ART initiation and throughout treatment are essential, including and especially after 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, the benefits of switching after a single elevated viral load result for those receiving NNRTI-based regimens would lead to significant personal and public health benefits. For people living with HIV receiving a current regimen that is NNRTI-based, switching therapy should therefore be considered after a single elevated viral load result if treatment adherence is likely. For those who are not adherent, an elevated viral load result would likely be caused by poor adherence. An immediate therapy 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 *(67)*. The studies reported the prevalence of low-level viraemia ranging from 2.7% to 26.0% by using various definitions. Low-level viraemia was generally considered one or more viral load results for a single person 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. Viral loads between 50 and 200 copies/ml trend towards predicting future virological failure. Viral loads between 200 and 500 copies/ml significantly predicted future virological failure, with adjusted hazard ratios all above 1.

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 the integrase inhibitor raltegravir. 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 viral suppression and during or after episodes of low-level viraemia *(67)*.

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 is 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 *(67)*. 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 rolling review undertaken to update the Spectrum mathematical model *(68)* 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 events were 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

In many settings, reliance on dried blood spot, point-of-care technologies or other alternative specimen type or technology is necessary to expand 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 was variable (Table 1) *(41,69)*. Several technologies could perform to 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 viral suppression or undetectable 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 1. Diagnostic accuracy of alternative sample collection types (dried blood spot) or point of care with lower theoretical treatment failure thresholds

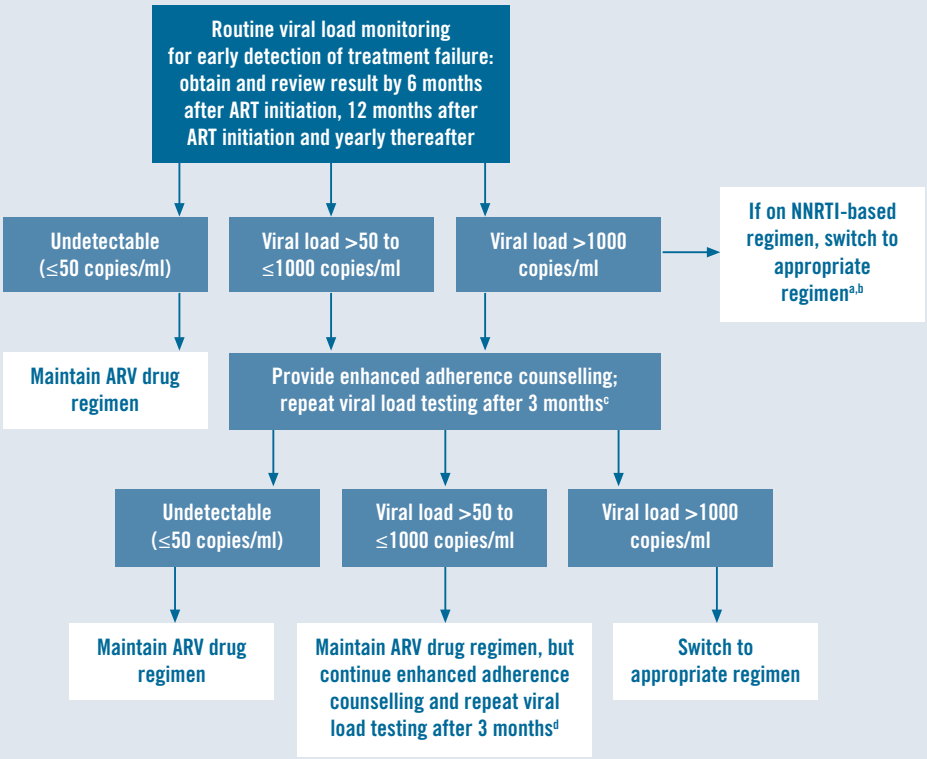
Sensitivity	Abbott 1-spot[a]	Abbott 2-spot[a]	Biocentric	Bio-Merieux[b]	Hologic[c]	Roche FVE[d]	Roche SPEX[d]	Siemens	Cepheid
1000	88 (50–98)	93 (84–97)	95 (71–99)	83 (78–87)	85 (44–98)	95 (85–98)	98 (96–99)	91 (69–98)	96 (95–97)
800	92 (5–100)	93 (83–97)	99 (44–100)	85 (80–89)	93 (31–100)	95 (87–98)	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)

Specificity	Abbott 1-spot[a]	Abbott 2-spot[a]	Biocentric	Bio-Merieux[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 grey shaded cells represent those with <85% sensitivity or specificity.
Sources: Sacks et al. *(42)*, Vojnov et al. *(69)* and Vojnov et al. *(70)*.

Fig 1. Treatment monitoring algorithm



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 if treatment experience is likely.
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 should be given priority across the laboratory referral process (including specimen collection, testing and return of results). See subsection 3.2.
d. Consider therapy switch for those receiving NNRTI-based regimens and based on clinical considerations and no adherence concerns.

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 viral suppression. 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 (see Box 2). 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 3 shows specific implementation considerations for treatment monitoring 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 viral suppression (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 viral suppression.

Research gaps

Several research considerations would be beneficial. These 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 off 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.

Box 3. Implementation considerations for treatment monitoring 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 1.
b. See the programmatic update on HIV diagnosis and ARV use in HIV-exposed infants *(24)*.
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 subsection 3.1.
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 (see the programmatic update on HIV diagnosis and ARV use in HIV-exposed infants *(24)*).

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4. CLINICAL GUIDELINES: TIMING OF ANTIRETROVIRAL THERAPY

4.1 Timing of ART for adults and children with TB

Recommendation

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 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.

Background

TB remains the leading cause of mortality among people living with HIV, despite substantial scale-up of ART, accounting for 30% of the AIDS-related deaths reported in 2019 *(1)*. Since 2010, WHO has recommended that ART be started as soon as possible and within eight weeks of initiating TB treatment (strong recommendation, high-quality evidence), and in 2013, 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) *(2)*. In 2017, based on a systematic review of evidence that earlier ART initiation resulted in reduced morbidity and mortality *(3)* (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 *(3)*, with stated cautions for those with signs and symptoms of meningitis and a brief delay if TB suspected.

WHO HIV guidelines adopt a public health approach, which includes simplifying and harmonizing recommendations across populations; however, the guidance on the timing of ART initiation is not aligned among people living with HIV starting TB treatment. In addition, ART regimens (including integrase inhibitors such as DTG and raltegravir) promise improved efficacy, safety and tolerability; but current guidance on the timing of ART is based on evidence from older ART regimens. Finally, there has been progressive country-level policy evolution towards earlier initiation of ART among people starting TB treatment. Several countries in Africa have moved beyond the 2016 WHO guidelines *(2)*, recommending ART initiation within two weeks of TB treatment start regardless of CD4 count, including among children (except for tuberculous meningitis). Current practice for children living with HIV in many settings has also shifted to promote the early initiation of ART.

Given the recommendation to rapidly initiate ART for most people living with HIV *(3)* in the interest of simplifying programmes and to minimize pre-ART loss to follow-up, the question posed is whether the current recommendation of timing of ART following TB treatment initiation should be updated and applied to all people living with HIV, including children, regardless of CD4 cell count. A systematic review was undertaken to compare ART initiation within two weeks of TB treatment start with ART initiation between two and eight weeks after initiating TB treatment as well as among people living with HIV with CD4 counts above and below 50 cells/mm^3.

Rationale and supporting evidence

Background

The systematic review conducted for this guideline (see Web Annexes) was similar to the review conducted in 2015, with the addition of CD4-disaggregated data that were not previously available for two studies from 10 randomized controlled trials *(4–13)* and of an unpublished trial *(13)*. Four studies *(6,8,12,13)* provided information on ART initiation within two weeks of TB treatment start 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.

Although the 2015 review compared ART initiation within two weeks, within eight weeks and after eight weeks of TB treatment initiation (eight weeks reflecting the intensive phase of TB treatment), initiating ART within two weeks was not directly compared with between two and eight weeks after TB treatment initiation.

The limitations of the current review include all studies being completed before 2014 and a range of legacy ARV drug combinations that are no longer used. None of the trials included children and adolescents younger than 13 years; only two trials included adolescents 13 years and older, but there were not sufficient data to analyse this group separately. In addition, there were no data on pregnant and breastfeeding women.

Evidence was also limited regarding the timing of ART for those with drug-resistant TB, those receiving second- and third-line ART regimens and for serious adverse events: for example, it was unclear what proportions were related to drug–drug interactions, hepatotoxicity and immune reconstitution inflammatory syndrome.

Summary of review findings

The systematic review reports outcomes in terms of risk differences as the selected estimate of effect and associated absolute measures per 100 people.

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 count less than or equal to 50 cells/mm3, low-certainty evidence indicated that mortality may be reduced (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 greater than 50 cells/mm3, 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 less person with viral load suppression 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 of increased risk of immune reconstitution inflammatory syndrome in DTG-based regimens, the INSPIRING trial *(14)* reported that the incidence of immune reconstitution inflammatory syndrome was similar between the DTG and EFV arms (a 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 *(15)*. The REALITY trial for advanced HIV disease included raltegravir as an additional option and also did not find any increased incidence of immune reconstitution inflammatory syndrome *(16)*. Box 4 details specific considerations for cryptococcal and TB meningitis.

Box 4. 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 cryptococcus, earlier ART is associated with more severe adverse events and increased mortality with cryptococcal meningitis. For people living with HIV with 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 *(17)*.

[b] Guidelines for treatment of drug-susceptible tuberculosis and patient care (2017 update) *(18)*.

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 extend the overall recommendation of earlier initiation to children, acknowledging the very low-quality evidence resulting from considerable indirectness. The Guideline Development Group highlighted the urgency of initiating ART in this subgroup, especially young children *(19)*. Strong evidence indicates increased morbidity and mortality when ART initiation is delayed among infants and young children regardless of CD4 cell count *(20)*. In terms of harm, the overall incidence of immune reconstitution inflammatory syndrome appears to be low among young children initiating ART, and recent studies have reported few deaths *(21,22)*. It was also acknowledged that there has been an important shift in clinical practice towards earlier ART initiation among children with TB, without any reported increase in the incidence of immune reconstitution inflammatory syndrome. This combined with better capacity to diagnose and manage TB immune reconstitution inflammatory syndrome among children and very low mortality reported in this subgroup are overall reassuring findings that support the recommendation.

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. Eswatini, Kenya and Nigeria also have similar policies.

This evolution of policies suggests that adopting and implementing the intervention is feasible. In addition, case studies from Eswatini, Malawi and Uganda support the feasibility of earlier initiation of ART for people with both TB and HIV *(23)*.

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 *(24)*. The acceptability of this intervention was not assessed for specific subpopulations. Although uncertainty remains regarding any difference in patient and health-care worker preferences for children, adolescents and pregnant or breastfeeding women, major differences were deemed to be unlikely.

In preparation for the 2020 guidelines, WHO conducted a survey of values and preferences(see Web Annexes) 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. There were some concerns regarding complications of TB immune reconstitution inflammatory syndrome with same-day initiation of ART and TB treatment among health-care workers and programme managers. One limitation of the survey was the small sample size, and it may not capture the full spectrum of views on health-care worker preferences. Guideline Development Group members also informed the values and preferences judgements from their own experience and observations.

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 cell count, including children. In addition, given current recommendations for rapid ART initiation, denying earlier ART to those with TB could introduce significant inequities unless the decision is based on a very strong rationale or potential for substantial harm.

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 cell count, among adults based on low- to moderate-certainty evidence and a conditional recommendation for children and adolescents based on very-low-certainty evidence. This decision was based on reviewing the evidence, considering the known overall benefits of early ART initiation and concluding that the lack of difference between the earlier (within two weeks) and later (two to eight weeks) ART initiation groups in reducing mortality outweighed the potential harm from the potentially increased incidence of immune reconstitution inflammatory syndrome and hospitalization. This decision was applicable to all people living with HIV regardless of CD4 cell count (except for those with signs and symptoms of meningitis).

The Guideline Development Group acknowledged that the current use of less toxic HIV treatment options, such as DTG-based ART, are well tolerated, efficacious and available as a fixed-dose combination, reduces potential concerns related to pill burden, toxicity and drug–drug interactions (with appropriate adjustment of dosing with rifamycins), and the review results can be extrapolated to newer regimens. In addition, earlier ART initiation is expected to increase equity across populations and negligibly affect programme costs and is the preferred treatment option among people living with HIV. These considerations combined with the proven feasibility of implementing earlier ART in many settings were key drivers of the recommendation.

Implementation considerations

People should be closely followed up to monitor adverse events related to co-treatment, immune reconstitution inflammatory syndrome, including paradoxical TB 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. HIV programmes must plan to address specific known interactions between rifamycins and ARV drugs, such as the need to forecast and procure single 50-mg DTG tablets for the period of co-treatment. 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 *(25,26)*.

The Guideline Development Group also discussed the PredART study *(27)*, which examined the prophylactic use of prednisone to prevent paradoxical TB immune reconstitution inflammatory syndrome among 240 adults living with HIV with CD4 cell count <100 cells/mm3 with TB initiating ART (within 30 days of TB treatment) in a setting with a high burden of TB and HIV. The study reported high rates of paradoxical TB immune reconstitution inflammatory syndrome (47% in the placebo group and 33% in the prednisone group) and of hospitalization (25%) but very few deaths; and a recently published sub-study of the PredART study found that prophylactic prednisone did not affect pulmonary outcomes *(28)*. The prophylactic use of corticosteroids has not been fully examined with earlier ART start, and the Guideline Development Group agreed that more data are needed to understand the role of corticosteroids in this context. Enhanced monitoring and active surveillance of emerging toxicity and drug–drug interactions are critical for addressing potential safety concerns.

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. Since many countries are already implementing policies of earlier ART initiation, cohort analyses of TB and HIV outcomes such as TB immune reconstitution inflammatory syndrome, hospitalization, adverse events, loss to follow-up and viral load suppression are desirable. More data on the use of corticosteroids for people living with HIV who have low CD4 cell counts to prevent immune reconstitution inflammatory syndrome, especially in meningeal TB infection and occurrence of central nervous system immune reconstitution inflammatory syndrome is needed. Finally, more research on multi-disease treatment adherence support and the engagement of communities is needed.

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4.2 Updated clinical considerations for rapid ART initiation

A systematic review was conducted to address the applicability of a minimum set of TB exclusion criteria (signs and symptoms) to enable same-day ART initiation among people newly diagnosed with HIV. The review (see Web Annexes) *(1)* identified four studies that met the inclusion criteria, but none directly addressed the question. However, the review findings did indicate that same-day ART initiation for people with symptoms suggesting TB was feasible. After examining the above evidence, the Guideline Development Group agreed that, rather than pursue a new recommendation, WHO would further articulate the implementation of and clinical considerations for rapid ART initiation (Box 5).

The Guideline Development Group supported the revision of the existing statement suggesting a brief delay in ART initiation for individuals who had a positive TB symptom screen except for people who have signs or symptoms of meningitis (Box 4).

Box 5. Clinical considerations for people living with HIV being evaluated for rapid ART initiation

The Guideline Development Group suggested the following update to existing guidance on rapid ART initiation *(2)*:

- **previous clinical consideration:** brief delay in ART initiation while investigating for TB symptoms; and
- **new clinical consideration:** 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.

Caution is needed for people living with HIV who have tuberculous meningitis, since immediate ART is associated with more severe adverse events than initiating ART two months after TB treatment starts. If tuberculous meningitis or cryptococcal meningitis is suspected clinically (signs and symptoms) or confirmed with laboratory testing, ART should be delayed.

Background and rationale

TB is the most common cause of morbidity and mortality among people living with HIV, accounting for 30% of all HIV-associated deaths in 2019 *(3)*, and earlier ART initiation has been shown to reduce morbidity and mortality overall and from TB. Rapid ART initiation has been recommended by WHO (since 2017) and should be offered to all people living with HIV following a confirmed HIV diagnosis with clinical assessment (within a week) and on the same day to people who are ready to start *(4)* (strong recommendation, high-certainty evidence for adults and adolescents and low-certainty evidence for children). Several good practice statements included evaluation of signs and symptoms suggesting TB and meningitis before rapid ART initiation, and ART should be delayed for individuals who are being investigated for TB symptoms, arising as concern about the risk of increased cases of paradoxical TB immune reconstitution inflammatory syndrome.

TB symptoms, as defined by the WHO-recommended four-symptom screening *(5,6)*, are the presence of any of the following: a current cough, fever, weight loss or night sweats. These would preclude same-day ART initiation. Despite a global push to scale up ART and implement rapid ART policies, recent studies in Kenya and South Africa *(7)* indicate that many individuals, nearly half in one study, presenting for initial assessment are not eligible for same-day ART, primarily because of active TB disease or signs and symptoms suggesting TB requiring further investigation, with most yielding negative test results for TB *(7)*. Further, a 2018 WHO-commissioned review found there was lower sensitivity of the WHO four-symptom screening approach among people with HIV who are on ART, compared to those who were ART naïve. This found that the WHO four-symptom screening had a sensitivity of 89.4% and a specificity of 28% compared with a culture reference standard. This would mean there would be an increased number of false positives and would necessitate further TB investigations and unnecessarily delay ART start *(8)*. This missed opportunity for early ART initiation could potentially increase pretreatment loss to follow-up and increase overall morbidity and mortality because of delayed ART initiation. WHO guidelines on systematic screening of TB is currently in the process of being revised and updated guidance is expected soon *(9)*.

Although there are important concerns about developing TB-immune reconstitution inflammatory syndrome, little information is available in the published literature on mortality related to ART initiation among people with undiagnosed TB, especially at low CD4 cell counts. Some researchers have suggested a more "permissive" approach that allows initiation of ART among people living with HIV with TB symptoms (or a minimum set of criteria) while investigating for TB *(10)*. However, the TB signs and symptoms that would enable safe same-day ART initiation while minimizing the risk of immune reconstitution inflammatory syndrome are not known. Conversely, the signs and symptoms that would preclude safe same-day ART initiation are also unknown.

Summary of available evidence

The systematic review conducted to address this research question 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. All four (RapIT trial *(11,12)*, SLATE I *(7)*, SLATE II *(10)* and CASCADE *(13)*) focused on rapid ART initiation, randomized to compare time to ART initiation between the intervention group and the standard of care; however, to examine TB screening approaches, only data from the intervention arms were relevant to this review. No studies compared two or more TB screening algorithms with each other, and there was no direct information on the outcomes of people who started same-day ART in the presence of unknown TB disease (without TB treatment). A meta-analysis was not possible, and thus a narrative review was conducted. The main findings from these small studies was 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 (SLATE II and CASCADE). The SLATE II trial in South Africa assessed 296 people living with HIV with the WHO four-symptom screening and used the presence of "mild" TB symptoms as determined by clinicians and a negative urine lipoarabinomannan test as part of an algorithm to determine eligibility for same-day ART. A total of 87% were able to initiate ART on the same day (with only 2% diagnosed with TB). In the community-based CASCADE trial in Lesotho, 137 people living with HIV were assessed for same-day ART initiation at home. The WHO four-symptom screening was administered and, if positive, a sputum sample was sent for a molecular diagnostic test; however, all people living with HIV were permitted to initiate same-day ART regardless of TB symptoms except for suspected TB meningitis. A total of 98% were able to initiate same-day ART, only 7% had TB symptoms at baseline and none had diagnosed TB.

The conclusion of the review was that there is no direct evidence to answer the question and very little information available on the potential harm of same-day ART initiation in the presence of TB symptoms; however, these small studies support the feasibility of this approach. Substudies to the SLATE trials have reported on the acceptability of same-day initiation, with 95% satisfaction with care, and also that same-day initiation with "mild" TB symptoms was acceptable to patients and providers; and evidence indicates that, overall, among people living with HIV (unknown TB status), same-day start is acceptable and recommended by WHO *(14)*. 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 suggests that this approach is feasible *(15)*. A case study from the Martin Preuss Centre (Lighthouse Trust) in Lilongwe, Malawi reported a practice of initiating same-day ART among people living with HIV who are considered to be "stable" regardless of TB symptoms (at the discretion of clinicians, if not severely ill) *(14)*; however, there are very limited cohort data reporting relevant outcomes.

Discussion and conclusion

Based on clinical experience and the expert opinion of the Guideline Development Group, a proposed revision of the clinical considerations related to TB symptoms and rapid ART initiation was made. The group noted that the existing good practice statement to delay ART in individuals with TB symptoms may result in harm because of delays in ART initiation and increase the risk of pretreatment loss to follow-up. The Guideline Development Group also felt that it would be important to maintain consistency with the new strong recommendation that ART should be initiated within two weeks of initiating TB treatment (see subsection 4.1) to further harmonize WHO normative guidance for HIV treatment.

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 cryptococcus infection among those with advanced HIV disease before initiating ART, since immune reconstitution inflammatory syndrome among these people is more common and potentially life-threatening. Box 5 shows the new language and clinical considerations for people living with HIV being evaluated for rapid ART initiation.

Implementation considerations

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 *(16)*. 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. Improvements in case-based surveillance systems are required to identify those who are lost to follow-up and who experience adverse events and immune reconstitution inflammatory syndrome.

Research priorities

Research gaps include the impact of initiating ART among people with TB symptoms (excluding those with signs and symptoms of meningitis) on mortality, TB and HIV outcomes, adverse events, immune reconstitution inflammatory syndrome, retention in care and adherence, including the impact among children, pregnant and breastfeeding women. Analysing routine programme data in countries implementing this approach would be helpful as well as studies to understand how to optimize the implementation of this approach, including among people with advanced HIV disease. The Guideline Development Group suggested one key research gap is to examine the role of prophylactic corticosteroids to reduce the incidence of immune reconstitution inflammatory syndrome among people with TB and HIV in public health settings and the timing of prophylaxis. Although adjuvant corticosteroids are recommended for tuberculous meningitis, they are not recommended for people living with HIV with cryptococcal meningitis, so refining clinical approaches to using corticosteroids among people living with HIV with meningitis is critical.

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5. DISSEMINATING, ADAPTING AND IMPLEMENTING THE GUIDELINES

The Department of Global HIV, Hepatitis and Sexually Transmitted Infection Programmes is working with the WHO Press to ensure maximum visibility of WHO products at major conferences, such as the International AIDS Society conferences and the Conferences for Retroviruses and Opportunistic Infections. Following approval by the Guidelines Review Committee, the updated guidelines will be made available on the WHO HIV website. The recommendations developed for this guideline, as well other relevant guidance released since 2016, will be integrated into the updated consolidated HIV guidelines planned for release in July of 2021. The publication will be made available in English. Translations to other official languages will be developed in coordination with the regional and country offices.

Media and formats

The recommendations and supporting information will be integrated into the WHO HIV Tx App[11] which is a free mobile application for easy access and reference. The App is available globally for download on major App stores. Printed materials, pdfs and social media links will also be available to disseminate key messages of WHO recommendations. Key annexes containing information on the systematic reviews and other supporting information will be uploaded to the WHO website. Derivative products will be produced to assist countries in adapting and implementing guidelines into their own context in the form of slide sets, question and answers (Q&A) and webinars with key stakeholders.

Implementation

The Department of Global HIV, Viral Hepatitis and Sexually Transmitted Infection Programmes monitors the uptake of HIV-related recommendations through several mechanisms, including the Global AIDS Monitoring framework, in-country surveys and population-based HIV impact assessments, which provides indirect evidence of the impact of WHO recommendations. The Department will be working with the WHO regional and country offices to monitor the uptake and implementation of the WHO guidelines. Potential barriers include delays in dissemination because of increased time to translate the document and delayed uptake because of limited resources in countries to change existing policies.

Updating

The guidelines will be updated in a modular process. Ongoing scoping reviews are carried out to anticipate what guidance might be required for the coming years. When necessary, rapid guidance and technical and operational updates will complement the guideline updates.

[11] Weblinks: www.hivtx.org/iphone, www.hivtx.org/android

ANNEXES

Annex 1. Process for developing the clinical guideline

Background

The WHO 2013 consolidated guidelines for antiretroviral therapy combined recommendations across the continuum of HIV care for the first time. This was updated in 2016. Since then, growing evidence in clinical and operational studies necessitated developing updated normative guidance. Several supplementary guidelines have been published with a modular approach to address the emerging evidence. Table A1 summarizes key normative guidance released since 2016 up to the time this document was written, mapped to the relevant chapters of the 2016 consolidated guidelines. The recommendations developed for this guideline will be integrated with the updated consolidated HIV guidelines in 2021. The updated consolidated guidelines will also contain updated recommendations for service delivery, which is subject to a separate guideline development process.

Table A1. Summary of key normative guidance released and ongoing since 2016, mapped to the corresponding chapters of the consolidated guidelines

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection		
Chapter	**Key guidance between 2016 and 2020**	**Latest / upcoming guidance**
2. HIV diagnosis	Consolidated guidelines on HIV testing services for a changing epidemic November 2019 Updated recommendations on early infant diagnosis of HIV December 2018	Updated recommendation on using point-of-care infant diagnosis (see subsection 3.1)
3. Prevention	Preventing HIV through safe voluntary medical male circumcision for adolescent boys and men in generalized HIV epidemics August 2020 Updated recommendations on post-exposure prophylaxis December 2018	New recommendation on the dapivirine vaginal ring as a prevention option (see subsection 2.1)
4. HIV treatment and monitoring	Update of recommendations on first- and second-line antiretroviral regimens July 2019 Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy July 2017	Updated recommendation on use of point-of-care viral load testing (see subsection 3.2) Revised treatment monitoring algorithm (see subsection 3.3) New recommendation and updated clinical considerations for TB and HIV in the context of when to start antiretroviral therapy (see section 4.1 and 4.2)

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection		
Chapter	**Key guidance between 2016 and 2020**	**Latest / upcoming guidance**
5. Comorbidities	Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV April 2020 Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children March 2018 Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection July 2018 Guidelines on hepatitis B and C testing February 2017	See TB and HIV recommendations above in the context of when to start antiretroviral therapy Other guidelines processes that are ongoing include: cervical cancer, sexually transmitted infections, physical activity and sedentary behaviour and adolescent mental health
6. Service delivery	Maintaining and improving quality of care within HIV clinical services July 2019	Ongoing parallel guidelines process to update several recommendations within this chapter
7. Toxicity, HIV drug resistance, monitoring and evaluation	Consolidated guidelines on person-centred HIV patient monitoring and case surveillance June 2017 Tackling HIV drug resistance: trends, guidelines and global action July 2017 Biobehavioural survey guidelines for populations at risk for HIV September 2017 Consolidated HIV strategic information guidelines: driving impact through programme monitoring and management April 2020	No new recommendations. The consolidated strategic information guidelines are being updated and planned for released in late 2021
Cross-cutting guidelines	Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations July 2016 Consolidated guideline on sexual and reproductive health and rights of women living with HIV March 2017	Maternal, newborn and child health guidance for women living with HIV

A hub-and-spoke approach was used to assign specific topic areas to relevant WHO staff members across all areas of work in HIV to conduct consultations and scoping reviews (Fig. A1). This guideline primarily deals with clinical topics.

Several technical scoping meetings were held to formulate the population, intervention, comparison and outcome (PICO) questions relevant to this guideline document as well as from research gaps highlighted from previous guideline meetings. Table A2 summarizes these activities.

Fig. A.1 Hub-and-spoke model for technical scoping conducted for the guidelines update

Table A2. Technical scoping meetings to inform the clinical guideline update

Details of scoping meetings held	Date
HIV and TB scoping consultation	2019
HIV treatment transition and drug sequencing in the context of new antiretroviral drugs (at the Conference on Retroviruses and Opportunistic Infections): think tank https://www.who.int/hiv/pub/meetingreports/think-tank-HIVtreatment-croi2017/en	2017
Partners synergy meeting	2017
WHO Meeting on Treatment and Monitoring Optimization of HIV (at the Conference on Retroviruses and Opportunistic Infections) https://www.who.int/hiv/pub/meetingreports/arv-optimization-2018/en	2018
Technical consultation on infant testing and prophylaxis	2018
Viral load virtual guideline preparation meetings	2020
HIVResNet meeting https://www.who.int/publications/i/item/who-hivresnet-2018-meeting-report	2018
Paediatric Antiretroviral Working Group (PAWG) meeting	Regular meetings are held through the year

To update this guidance, a Guideline Development Group meeting was convened virtually because of the COVID-19 global health crisis. This group met everyday via video teleconferencing from 28 spetmeber until 2 october 2020. The standard GRADE (Grading of Recommendations Assessment, Development and Evaluation) and PICO process for guideline development was used for this clinical guideline development process. Seven systematic reviews were undertaken to address the PICO questions formulated. These were complemented by supporting information from sources, including an online values and preferences commissioned by WHO and targeted literature reviews on feasibility, acceptability, costs and resources, cost–effectiveness and disease modelling.

Retrieving, summarizing and presenting the evidence

Quantitative evidence synthesis and evidence to recommendations

The GRADE method was used to rate the certainty of the evidence and determine the strength of the recommendations. The GRADE approach to developing recommendations, which WHO has adopted, defines the certainty of evidence as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence match the actual effects of interest. The strength of a recommendation reflects the degree to which the Guideline Development Group is confident that the desirable effects (potential benefits) of the recommendation outweigh the undesirable effects (potential harm). Desirable effects may include beneficial health outcomes (such as reduced morbidity and mortality), reduction of burden on the individual and/or health services and potential cost savings. Undesirable effects include those negatively affecting individuals, families, communities or health services. Additional considerations include the resource use and cost implications of implementing the recommendations and resultant clinical outcomes (such as drug resistance and drug toxicity), the values and preferences of those affected by the recommendations, the feasibility and acceptability of the interventions and how implementation affects equity and human rights.

All systematic reviews followed the PRISMA guidelines for reporting systematic reviews and meta-analyses. The outputs of the meta-analysis were displayed as relative estimates based on the review in consideration (except for the early versus late ART initiation among people living with HIV with TB, which presented risk differences), and the effect size was also shown for each outcome in absolute terms – per 1000 people – along with the GRADE level of certainty of evidence (high, moderate, low and very low) for each outcome in GRADE evidence profile tables. The respective reviewers developed the systematic reviews with input from WHO by sharing drafts for comment, and the final outputs were discussed in detail with the methodologist for the meeting to ensure that the outputs were in the appropriate form and interpretation for use in the Guideline Development Group meeting. Using an electronic survey, the Guideline Development Group ranked the importance of each systematic review outcome using the GRADE rating scale (1–9).[12] The Guideline Development Group made the final decision regarding the overall GRADE certainty rating for each PICO (see Table A3) by considering the consistency of the critical outcomes and selecting the highest rating for which the results were consistently beneficial across outcomes or the lowest rating for which the results were inconsistent.

Table A3. Summary of PICO questions

PICO question	Summary of systematic review methods
PICO 1: *Should the dapivirine vaginal ring be offered as an additional prevention choice for women at substantial risk of HIV infection as part of combination prevention approaches?*	**Review type:** Systematic review and meta-analysis **Review lead:** Medical University of South Carolina, USA **Search dates:** 1 January 2010 to 3 August 2020 **Databases searched:** PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature) and EMBASE **Number of studies and study design:** Five studies were included, comprising data from 10 articles and 8 conference abstracts, including one Phase IIb safety study, two randomized controlled trials and two open-label extension trials.
PICO 2: *Should point-of-care nucleic acid testing technologies be used to diagnose HIV among infants and children younger than 18 months of age compared with laboratory-based testing?*	**Review type:** Systematic review and meta-analysis **Review group:** Global Health Impact Group Team, Atlanta, USA **Search dates:** January 2014 to August 2020 **Databases searched:** PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Conference Proceedings Citation Index-Science (CPCI-S) and WHO Global Index Medicus **Number of studies and study design:** The review identified seven studies, two randomized controlled trials and five cohort studies.
PICO 3: *Among people living with HIV who are initiating or receiving ART, is point-of-care molecular HIV viral load monitoring associated with improved management and patient outcomes compared with laboratory-based viral load monitoring?*	**Review type:** Systematic review and meta-analysis **Review lead:** University of Cape Town, South Africa **Search dates:** through August 2020 **Databases searched:** PubMed/MEDLINE, EMBASE, Cochrane Registers of Diagnostic Test Accuracy Studies and Clinical Trials, WHO Global Index Medicus and conference databases (Conference on Retroviruses and Opportunistic Infections, International AIDS Society and African Society for Laboratory Medicine) **Number of studies and study design:** 35 were included (three systematic reviews reporting on test accuracy, 29 original research reports from 28 studies, and three programmatic reports). Clinical data were reported in six publications and one conference poster, including one randomized clinical trial, two non-randomized studies and four single-cohort studies describing outcomes following point-of-care monitoring.

[12] WHO handbook for guideline development. 2nd ed. Geneva: World Health Organization; 2014.

PICO question	Summary of systematic review methods
PICO 4: *Should the HIV viral load testing algorithm outlined in the 2016 WHO consolidated guidelines be modified?* *a) Should the first viral load be done 1 or 3 months after ART initiation (versus 6 months)?* *b) For people with an elevated viral load, should the repeat viral load be performed earlier (1 month later versus 3–6 months later)?* *c) Should people receiving efavirenz-based ART with an elevated viral load be switched immediately to second-line ART without a repeat viral load?* *d) Should the HIV viral load treatment failure threshold be lowered from 1000 copies/ml? If so, to what number of copies/ml?*	**Review type:** Supportive evidence reviews per subquestions **Review lead:** Global Health Impact Group Team, Atlanta, USA **Search dates:** January 2005 to June 2020; Conference on Retroviruses and Opportunistic Infections and International AIDS Society and abstracts from 2017 to 2020 **Databases searched:** a, b, c and d: EMBASE, PubMed/MEDLINE and conference databases (Conference on Retroviruses and Opportunistic Infections and International AIDS Society); d: Cochrane Central Register of Controlled Trials, Conference Proceedings Citation Index-Science and WHO Global Index Medicus **Number of studies and study design:** The main research question yielded no results following a systematic review approach. The subquestions asked yielded the following: a) Eight randomized controlled trials among adults and two randomized controlled trials among children. An observational study of advanced HIV disease also summarized but not included in the pooled analysis b) Of the 25 studies summarized, 20 were retrospective and five were prospective. Most studies involved adults, one adolescents and two children. c) Of the 31 included studies, 16 studies were relevant to virological failure and/or disease progression, eight studies examined drug resistance (cohort studies) and seven studies looked at HIV transmission. d) Nine national surveys of acquired drug resistance among adults. One systematic review (66 studies included) and one prospective cohort study.
PICO 5: *When should ART be initiated for people living with HIV who are receiving (have recently initiated) treatment for TB?*	**Review type:** Systematic review **Review team**: London School of Hygiene and Tropical Medicine & Liverpool School of Tropical Medicine, United Kingdom **Search dates:** 1 January 2003 to 12 March 2020 **Databases searched:** EBSCO Africa-wide information, EBSCO CINAHL Plus, Wiley Cochrane Central Register of Controlled Trials, OvidSP Embase, OvidSP Global Health, World Health Organization Global Index Medicus, OvidSP Medline ALL, and Clarivate Analytics Web of Science Citation Index **Number of studies and study design:** Ten randomized controlled trials and one unpublished trial were included
PICO 6: *What are the minimum exclusion criteria (TB signs and symptoms) for same-day ART initiation for people newly diagnosed with HIV?*	**Review type:** Systematic review **Review team:** London School of Hygiene and Tropical Medicine and Liverpool School of Tropical Medicine, United Kingdom **Search dates:** Varied by database to 12 March 2020 **Databases searched:** Ebsco Africa-Wide Information; Ebsco CINAHL Plus; Wiley Cochrane Central Register of Controlled Trials, Issue 3 of 12, 2020; OvidSP Embase, 1974 to 2020 March 11; OvidSP Global Health, 1910 to 2020 Week 09; World Health Organization Global Index Medicus; OvidSP Medline ALL, 1946 to March 10, 2020; Clarivate Analytics Web of Science, Science Citation Index Expanded, 1970 to 2020-03-11. Clinical trials registers: Clinical Trials.gov and World Health Organization International Clinical Trials Registry Platform **Number of studies and study design:** Four observational studies

Ethics

A report on key issues of equity, social justice and solidarity was developed with a particular focus on the point-of-care infant diagnosis and viral load questions. An ethicist was present at the Guideline Development Group meeting to present the key ethical issues concerning infant diagnosis and viral load monitoring and conduct a facilitated discussion on these issues.

Acceptability and values and preferences

WHO commissioned a global survey on feasibility, acceptability and values and preferences and distributed it to people living with HIV, health-care workers and programme managers with the support of civil society networks. The survey contained closed and open-ended questions and was made available between 6 July 2020 and 19 September 2020. The data were analysed using STATA 15.0 and the results analysed by a qualitative scientist. Despite the efforts, there was low response to the survey, and the results should be interpreted with this in mind. Qualitative studies were also reviewed as part of the quantitative systematic reviews carried out for these guidelines.

Feasibility

Evidence on feasibility was identified as part of the systematic review to inform point-of-care infant diagnosis, viral load testing and the treatment-monitoring algorithm (specifically for using dried blood spots and point-of-care testing with lower thresholds). Point-of-care device placement for infant diagnosis and viral load measurement (in countries in which devices have already been procured and delivered) was evaluated to understand the incremental cost. To better understand the realistic incremental costs for implementing point-of-care infant diagnosis in a set of countries, an affordability analysis was carried out, taking into account the country's laboratory network and point-of-care testing technologies already in place. To inform the question on point-of-care infant diagnosis, infant distribution in four countries was evaluated to determine the extent and need of devices to access 70% or 80% of all infants. The global survey mentioned under the subheading "Acceptability and values and preferences" also included questions for health-care workers, programme managers and people living with HIV on the feasibility of implementing various interventions. Several health ministry officials from national HIV programmes also provided input on programmatic data and experiences to inform feasibility in settings with a high burden of HIV.

Resource use and cost–effectiveness

The systematic reviews captured available information from published evidence on resource use, including costing, cost–effectiveness and affordability data. A systematic review of mathematical modelling studies was carried out on the cost–effectiveness of point-of-care nucleic acid testing for infant diagnosis of HIV. Further, a modelling synthesis of modifications in viral load monitoring in the context of sub-Saharan Africa was carried out. The Guideline Development Group and External Review Group included representatives from national programmes, who also provided perspectives on resource implications in their countries.

Guideline Development Group meeting

For the updated recommendations in 2020, the Guideline Development Group met virtually via Zoom teleconferencing from 28 September to 2 October 2020. Participants were required to register in advance to be able to attend the meeting and were required to identify themselves as members of the Guideline Development Group using the prefix "Guideline Development Group" to ensure they were distinct from other people on the call, which included WHO staff members and observers. The Group agreed at the start of the meeting that a majority of 60% of votes would be required if the Group had difficulty in making a recommendation for or against an intervention or for determining the strength of the recommendation. However, voting was not required during the meeting, and all recommendations were formulated through consensus. The systematic reviews and evidence-to-decision-making tables (Table A4 and the Web Annexes), prepared in accordance with the GRADE process, were shared in advance and presented at the meetings, and the methodologist facilitated discussions.

Table A4. Criteria for consideration in evidence-to-decision-making tables

Domain	Rationale
Certainty of the evidence	This is an assessment of the degree of confidence in the estimate of the effect: that is, the likelihood that the effect will differ substantially from what the research found. "Differ substantially" means a large enough difference that it might affect a decision.
Benefits and risks	When a new recommendation is developed, desirable effects (benefits) need to be weighed against the undesirable effects (risks), considering any previous recommendation or another alternative. The larger the gap or gradient in favour of the benefits over the risks, the more likely that a strong recommendation will be made.
Values of outcomes	This is a judgement of how much the people affected by an intervention or option value each of the outcomes. How much people value outcomes in relation to each other needs to be considered when weighing up the desirable effects of a treatment against the undesirable effects.
Cost and resource implications	How large the requirements are in resource use of the intervention and the alternative. Cost: the value of the resources that are consumed (such as staff time, drugs and use of equipment) as the consequences of an intervention or option. Cost–effectiveness: the cost of a treatment in relation to its effects. Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness is more likely to support a strong recommendation.
Equity	The absence of avoidable or remediable health differences among group of people that may be defined socially, economically, demographically or geographically.
Acceptability	How much a treatment or recommendation is accepted by the people who are affected by it or who are implementing it. If the recommendation is likely to be widely accepted or valued highly, it is likely that a strong recommendation will be made. A great deal of variability of strong reasons that the recommended course of action is unlikely to be accepted make a conditional recommendation more likely.
Feasibility	Is it feasible to implement an intervention and sustain it? If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.

Declarations of interest

All external contributors to the guidelines, including members of the Guideline Development Group and the External Review Group, completed a WHO declaration of interests form in accordance with WHO policy for experts. A brief biography of each Guideline Development Group member was published on the WHO HIV website for 14 days before the first meeting of the Guideline Development Group, with a description of the objectives of the meeting. No public comments or objections were received. The responsible technical officer reviewed the declaration of interest forms and the results of the web-based search for each member of the Guideline Development Group. The results were shared with the WHO Guideline Steering Group, which reviewed the results, and a management plan was agreed and recorded for each individual. At the start of the guideline development meeting, all conflicts of interest identified and the management plan for any conflicts of interest were shared with the meeting participants. In accordance with the revised WHO policy for experts, a web-based search was conducted of Guideline Development Group members to identify any potential competing interest. The WHO Guideline Steering Group recorded and reviewed the results of the web-based search to identify any potential competing interest. The declared conflicts of interest were summarized and presented at the start of the Guideline Development Group meeting, and members were asked to voice any additional conflicts or undeclared conflicts if previously undeclared. One Guideline Development Group member declared a potential conflict of interest from involvement as an author on a key study informing one of the systematic reviews and excused themselves from the decision-making process for that recommendation. No other conflicts of interest declared by the Guideline Development Group members warranted exclusion from the discussion of any of the recommendations.

External Review Group

The responsible technical officers reviewed the declaration of interest forms from members of the External Review Group in accordance with WHO guideline development policy, and the results were shared with the WHO Guideline Steering Group. Any conflicts of interest identified were considered when interpreting comments from External Review Group members during the external review process. In accordance with WHO procedures, all external reviewers signed a confidentiality agreement before reviewing the draft guidelines.

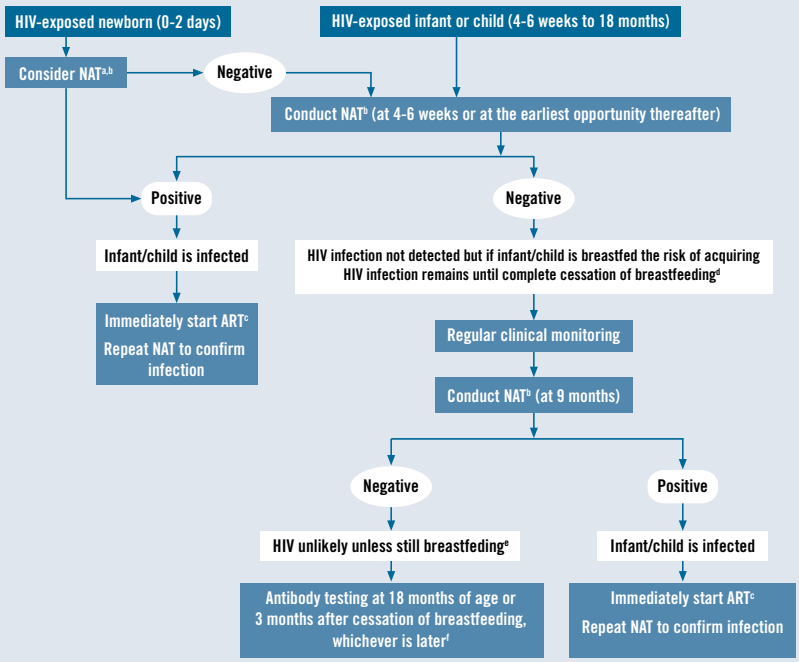
Peer review

The draft guidelines were circulated for review to members of the Guideline Development Group and the External Review Group in November 2020. The WHO Guideline Steering Group reviewed the comments and incorporated them into the final document, with due consideration of any conflicts of interest of External Review Group members.

Annex 2. Simplified infant diagnosis algorithm

The key principles for establishing whether HIV-exposed infants and children younger than 18 months are infected with HIV in low- and middle-income countries are as follows.

- Assess HIV exposure status by antibody testing the mother.
- Perform nucleic-acid testing for any HIV-exposed child who presents outside the national infant testing algorithm with clinical symptoms, regardless of previous nucleic-acid test results
- At nine months, perform nucleic-acid testing for HIV-exposed infants, symptomatic and asymptomatic, and even if previous nucleic-acid test results have been negative.
- Ensure that indeterminate test results are repeat tested immediately and given priority for rapid resolution.
- Ensure that confirmatory testing is undertaken following any positive result.
- Ensure regular follow-up for all HIV-exposed infants until final diagnosis, including providing co-trimoxazole prophylaxis and clinical and nutritional assessment.



Notes:

a. Based on *2016 WHO Consolidated ARV Guidelines*, addition of NAT at birth to the existing testing algorithm can be considered.
b. POC 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.

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