World Health Organization

GUIDELINES

GUIDELINE ON WHEN TO START ANTIRETROVIRAL THERAPY AND ON PRE-EXPOSURE PROPHYLAXIS FOR HIV

SEPTEMBER 2015

This early-release guideline will form part of the updated WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection due to be published in 2016.

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ABBREVIATIONS AND ACRONYMS

AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
FTC	emtricitabine
GRADE	grading of recommendations, assessment, development and evaluation
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
PICO	population, intervention, comparison and outcome
PMTCT	prevention of mother-to-child HIV transmission
PrEP	pre-exposure prophylaxis
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

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.

Age groups and populations

The following definitions for adults, adolescents, children and infants are used to ensure consistency within these guidelines. Other agencies may use different definitions.

- An **adult** is a person older than 19 years.
- An **adolescent** is a person 10–19 years old inclusive.
- A **child** is a person younger than 10 years old.
- An **infant** is a child younger than one year of age.

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.

Key populations are groups that have a disproportionate burden of HIV in many settings. They frequently face legal and social challenges that increase their vulnerability to HIV, including barriers to accessing HIV prevention and treatment. Key populations include (1) men who have sex with men, (2) people who inject drugs, (3) people in prisons and closed settings, (4) sex workers and (5) transgender people.

Vulnerable populations are populations that are vulnerable to HIV in certain situations or contexts, such as adolescents (particularly 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. Each country should define the specific populations that are vulnerable and key to their epidemic and response, based on the epidemiological and social context.

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. ART involves lifelong treatment.

Use of ARV drugs for HIV prevention refers to the HIV prevention benefits of ARV drugs and includes ARV drugs given to the mother or infant for preventing the mother-to-child transmission of HIV (PMTCT), ARV drugs to reduce the transmission of HIV among serodiscordant couples and ARV drugs to prevent people from acquiring HIV when they are exposed (post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP).

Viral suppression refers to a viral load below the detection threshold using viral assays.

Viral failure refers to the inability to achieve or maintain viral suppression below a certain threshold.

Treatment failure: the current WHO virological criterion for treatment failure is 1000 copies per ml or more.

Universal access to ART is defined broadly as a high level of access (80% or more of the eligible population) that is accessible and affordable. It does not necessarily mean 100% coverage.

Preventing the mother-to-child transmission of HIV: Previous WHO guidelines have used the terms "options A, B and B+" to refer to different approaches to preventing the mother-to-child transmission of HIV. The 2013 WHO guidelines recommended a choice between two approaches: (1) providing ART during pregnancy and breastfeeding to women who are otherwise not eligible for ART (option B) and (2) providing lifelong ART to all pregnant and breastfeeding women living with HIV regardless of CD4 count or clinical stage (option B+).

Service delivery

Continuum of HIV services refers to a comprehensive package of HIV prevention, diagnostic, treatment, care and support services provided for people at risk of or living with HIV and their families. Examples of these services include combination HIV prevention including pre-exposure prophylaxis; HIV testing and linkage to care; management of opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART; switching to second-line and third-line ART; and palliative care.

Continuum of HIV care refers to a comprehensive package of HIV services for people living with HIV.

A **public health approach** addresses the health needs of a population or the collective health status of the people rather than focusing primarily on individual case management. This approach aims to ensure the widest possible access to high quality services at the population level, based on simplified and standardized approaches, and to strike a balance between implementing the best-proven standard of care and what is feasible on a large scale in resource-limited settings. For HIV, key elements of a public health approach include simplified drug formularies; large-scale use of fixed-dose combinations for first-line treatment for adults, adolescents and children; care and drugs provided free at the point of service delivery; decentralization and integration of services, including task shifting; and simplified approaches to clinical monitoring.

HIV prevention

PrEP: Oral PrEP of HIV infection is the use of ARV drugs by HIV-uninfected people before the potential exposure to block the acquisition of HIV.

Substantial risk of HIV infection is defined by an incidence of HIV infection in the absence of PrEP that is sufficiently high (>3% incidence) to make offering PrEP potentially cost-saving (or cost-effective). Offering PrEP to people at substantial risk of HIV infection maximizes the benefits relative to the risks and costs. People at substantial risk of HIV infection are present in most countries, including some (but not all) people identified with key and vulnerable populations and some people not so identified.

Combination HIV prevention refers to a combination of behavioural, biomedical and structural approaches to HIV prevention to achieve maximum impact on reducing HIV transmission and acquisition.

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EXECUTIVE SUMMARY

In 2013, WHO published the first consolidated guidelines on the use of antiretroviral (ARV) drugs for HIV treatment and prevention across all age groups and populations. A comprehensive revision of these guidelines based on new scientific evidence and lessons from implementation is being undertaken in 2015.

This early-release guideline makes available two key recommendations that were developed during the revision process in 2015. First, antiretroviral therapy (ART) should be initiated in everyone living with HIV at any CD4 cell count. Second, the use of daily oral pre-exposure prophylaxis (PrEP) is recommended as a prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches. The first of these recommendations is based on evidence from clinical trials and observational studies released since 2013 showing that earlier use of ART results in better clinical outcomes for people living with HIV compared with delayed treatment. The second recommendation is based on clinical trial results confirming the efficacy of the ARV drug tenofovir for use as PrEP to prevent people from acquiring HIV in a wide variety of settings and populations.

The two recommendations are being made available on an early-release basis because of their potential to significantly reduce the number of people acquiring HIV infection and dying from HIV-related causes and significantly impact global public health. By publishing these recommendations as soon as possible, WHO aims to help countries to anticipate their implications in a timely fashion and begin the dialogue necessary to ensure that national standards of HIV prevention and treatment are keeping pace with important scientific developments.

The target audience for this guideline is primarily national HIV programme managers, who will be responsible for adapting the new recommendations at country level. The guideline will also be of interest to a wide range of other stakeholders, including national TB programme managers and civil society organizations, as well as domestic and international funders of HIV programmes.

The recommendations in this guideline will form part of the revised consolidated guidelines on the use of ARV drugs for treating and preventing HIV infection to be published by WHO in 2016. The full update of the guidelines will consist of comprehensive clinical recommendations together with revised operational and service delivery guidance to support implementation.

A Clinical Guideline Development Group convened by WHO developed the recommendations in this guideline based on systematic reviews that summarized the evidence available up to June 2015. The GRADE approach was used to determine the quality of the evidence and the strength of the recommendation.

The ambitious UNAIDS Fast-Track targets for 2020, including achieving major reductions in HIV-related mortality and new HIV infections and the 90–90–90 targets, will require countries to further accelerate their HIV responses in the coming years. Much greater effort is also needed to ensure that key and vulnerable populations and adolescents gain access to essential HIV treatment and prevention services. Implementation of the recommendations in this guideline will contribute to achieving these goals and to ultimately ending the AIDS epidemic as a major public health threat by 2030.

Summary of recommendations

The table below summarizes the recommendations presented in this guideline. The first recommendation on when to start ART among people living with HIV is subdivided into specific recommendations for adults, pregnant and breastfeeding women, adolescents 10–19 years old, children 1 to less than 10 years old and children younger than 1 year old.

Summary of recommendations in this guideline

Recommendation 1: When to start ART among people living with HIV			
Target population	**Specific recommendation**	**Strength of the recommendation**	**Quality of the evidence**
Adults[a] (>19 years)	ART should be initiated in all adults living with HIV at any CD4 cell count	*Strong*	*Moderate* NEW
	As a priority, ART should be initiated in all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Pregnant and breastfeeding women	ART should be initiated in all pregnant and breastfeeding women living with HIV at any CD4 cell count and continued lifelong	*Strong*	*Moderate* UPDATED
Adolescents (10–19 years old)	ART should be initiated in all adolescents living with HIV at any CD4 cell count	*Conditional*	*Low* NEW
	As a priority, ART should be initiated in all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤350 cells/mm^3	*Strong*	*Moderate*
Children (1 to <10 years old)	ART should be initiated in all children 1 to <10 years old living with HIV at any CD4 cell count	*Conditional*	*Low* NEW
	As a priority, ART should be initiated among all children <2 years old and those with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4% <25% (if <5 years old) or CD4 count ≤350 cells/mm^3 (if ≥5 years old)	*Strong*	*Moderate*
Children (<1 year old)	ART should be initiated in all children living with HIV younger than 1 year old at any CD4 cell count	*Strong*	*Moderate*

Recommendation 2: Oral pre-exposure prophylaxis to prevent HIV acquisition			
Target population	**Specific recommendation**	**Strength of the recommendation**	**Quality of the evidence**
HIV-negative individuals at substantial risk of HIV infection[b]	Oral PrEP (containing TDF) should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches	*Strong*	*High* NEW

[a] When this recommendation is fully implemented, the following WHO recommendations from 2013 will be superseded:

- TB and HIV coinfection: ART should be recommended for all people with TB who are living with HIV at any CD4 cell count *(strong recommendation, low-quality evidence).*
- HBV and HIV coinfection: ART should be initiated at any CD4 cell count if the person has severe chronic liver disease *(strong recommendation, low-quality evidence).*
- Serodiscordant couples: partners with HIV in serodiscordant couples should be offered ART at any CD4 cell count to reduce HIV transmission to uninfected partners (for preventing transmission) *(strong recommendation, high-quality evidence).*

[b] When this recommendation is fully implemented, the following WHO recommendations from 2012 and 2014 will be superseded:

- Serodiscordant couples (2012): Where serodiscordant couples can be identified and where additional HIV prevention choices for them are needed, daily oral PrEP (specifically tenofovir or the combination of tenofovir and emtricitabine) may be considered as a possible additional intervention for the uninfected partner *(conditional recommendation, high-quality evidence).*
- Men who have sex with men and transgender women (2012): In countries where HIV transmission occurs among men and transgender women who have sex with men and additional HIV prevention choices for them are needed, daily oral PrEP (either tenofovir or the combination of tenofovir + emtricitabine may be considered as a possible additional intervention *(conditional recommendation, high-quality evidence).*
- Men who have sex with men (2014): Among men who have sex with men, PrEP is recommended as an additional HIV prevention choice as part of a comprehensive prevention package *(strong recommendation, high-quality evidence).*

INTRODUCTION

01

1. INTRODUCTION

1.1 Health sector response to HIV

WHO first published guidelines on the use of antiretroviral therapy (ART) for HIV infection among adults and adolescents in 2002 *(1)* and on the use of antiretroviral (ARV) drugs for preventing the mother-to-child transmission of HIV in 2004 *(2)*. The 2006 updates of the guidelines *(3–5)* introduced the concept of a public health approach, with simplified and standardized ART regimens and clinical monitoring *(6)*. In 2013, WHO revised and combined these and other ARV-related guidance documents into one set of consolidated guidelines that addresses the use of ARV drugs for HIV treatment and prevention across all age groups and populations, based on the broad continuum of HIV care *(7)*. The 2013 consolidated guidelines are being updated in 2015 with a view to publishing new guidelines in 2016.

Since the guidelines were last revised in 2013, additional evidence has emerged to show that earlier use of ART results in better, long-term clinical outcomes for people living with HIV compared with delayed treatment. At the same time, most countries have recognized the operational and programmatic advantages of providing lifelong ART to all pregnant and breastfeeding women for both the long-term health of the mother and to prevent HIV transmission to the child. Clinical trial results have also confirmed the efficacy of the ARV drug tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), for use as pre-exposure prophylaxis (PrEP) to prevent people from acquiring HIV in a wide variety of settings and populations. The use of PrEP to prevent people from acquiring HIV is an important new prevention option for populations who are at a substantial risk of acquiring HIV. These results have been accompanied by strong recognition that more needs to be done to expand access to HIV treatment and prevention in the settings with the highest burden of HIV and among adolescents, key and vulnerable populations and in all epidemic settings.

1.2 Objectives

The objective of this guideline is to make available as soon as possible two new WHO recommendations that have emerged from the review process undertaken in 2015. These recommendations address (1) when to start lifelong antiretroviral therapy for people living with HIV and (2) PrEP to prevent people from acquiring HIV.

Implementing these recommendations at the national level will have important implications for programme priorities, funding and service delivery. Their early release will enable national HIV programmes to begin the dialogue necessary among national and international partners to expedite planning and implementation.

Rapid adoption and implementation of the recommendations in this guideline will also support the achievement of ambitious global goals and targets for HIV in the coming years, including the 90–90–90 targets[1] *(8)*. At the same time, they will help to ensure that the HIV response contributes strongly to the health components of Sustainable Development Goals, focusing on universal health coverage and providing all people the health services they need, of sufficient quality and without financial hardship, as set out in the WHO Global Health Sector Strategy on HIV 2016–2021 *(9)*.

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[1] 90% of people living with HIV know their HIV status; 90% of people living with HIV who know their HIV status are accessing ART; and 90% of people living with HIV receiving treatment achieve viral suppression.

The recommendations in this guideline will form part of the updated WHO consolidated ARV guidelines to be published in 2016. The complete guidelines will provide expanded operational and service delivery guidance to support implementation at the country level. They will provide guidance on effectively integrating HIV and other services and strategies to optimize quality along the continuum of HIV services, including adherence to treatment and retention in care.

1.3 Target audience

This guideline is primarily intended for use by national HIV programme managers. It will also be of interest to the following audiences:

- national HIV treatment and prevention advisory boards;
- national TB programme managers;
- national hepatitis programme managers;
- managers of maternal, newborn and child health and reproductive health programmes;
- clinicians and other health service providers;
- managers of national laboratory services;
- people living with HIV and community-based organizations; 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 this guideline and should guide the implementation of its recommendations.

- The guideline should contribute to and expedite the achievement of important global HIV and other health goals for 2016–2021.
- The guideline is based on a public health approach to scaling up the use of ARV drugs along the continuum of HIV prevention, treatment and care.
- In addition to strengthening the continuum of HIV services, the recommendations in the guideline should be implemented with a view to strengthening broader health systems, especially primary and chronic care.
- Implementation of the guideline needs to be accompanied by efforts to promote and protect the human rights of people in need of HIV services, including by ensuring informed consent, preventing stigma and discrimination in the provision of services and promoting gender equity.
- Implementation of the recommendations in this guideline should be informed by local context, including HIV epidemiology, availability of resources, the organization and capacity of the health system and anticipated cost–effectiveness.

1.5 Methods for developing the guidelines

1.5.1 Competing interests

All external contributors to the development of this guideline, including members of the Core Group, Clinical Guideline Development Group and External Review Group, completed a WHO

Declaration of Interests form. In accordance with the WHO Declaration of Interests policy for experts, a brief biography of each Clinical Guideline Development Group member was published on the WHO HIV website for a period of 14 days with a description of the objective of the meeting. No public comments or objections were received concerning the group membership.

The responsible technical officer reviewed all the Declaration of Interests forms completed by the Clinical Guideline Development Group members. A management plan for each declared conflict was agreed and recorded (Annex 1 includes the note for the record of the Declaration of Interests forms and management decisions). All declared interests and management strategies were discussed with the chairs and methodologist. Conflicts of interest were shared at the start of the Clinical Guideline Development Group meeting and participation closely monitored by the WHO Guideline Steering Group and GRADE methodologist. The majority of the Clinical Guideline Development Group did not declare significant conflicts of interest for this meeting.

Every effort was made to ensure that the representation of the Clinical Guideline Development Group minimized conflicts of interests. The Guideline Steering Group acknowledges that limiting the participation of key experts is challenging given the significant contribution of pharmaceutical companies in the field of HIV research and ARV drug trials and the participation of several experts as investigators in relevant trials.

The Guideline Steering Group assessed all completed Declaration of Interests forms for other external contributors to the guidelines. Individual participation was reviewed in respect of the interests declared. All Declaration of Interests forms are on electronic file at the WHO Department of HIV/AIDS and will be maintained for at least 10 years.

Grants from the Bill and Melinda Gates Foundation, United States Agency for International Development, United States Centers for Disease Control and Prevention and United States President's Emergency Plan for AIDS Relief provided funding for this guideline.

1.5.2 Guideline contributors

Three external review teams conducted systematic reviews to support this guideline. Annex 2 provides full details of the team leader and team members. Nandi Siegfried was the GRADE methodologist for this guideline.

An internal Guideline Steering Group of WHO staff and consultants coordinated the overall guideline development process. Meg Doherty and Rachel Beanland of the Department of HIV/AIDS led the Guideline Steering Group.

A Core Group of external experts provided strategic guidance to the guideline development process. Members of the Core Group also provided external review of the guideline.

An external Clinical Guideline Development Group convened by WHO reviewed evidence and developed the recommendations. The composition of the Clinical Guideline Development Group was in accordance with WHO procedures for developing guidelines *(10)* and included HIV experts, researchers, programme managers, epidemiologists, human rights experts, United Nations agencies and representatives of civil society organizations and networks of people living with HIV. Representatives from civil society were selected from a call for nominations; three participants were selected from more than 90 applications. The WHO HIV Civil Society Reference Group contributed to the selection process. Appropriate representation by region and sex was considered. The Co-Chairs of the Clinical Guideline Development Group also participated in the Core Group to ensure consistency.

WHO also recruited an External Review Group of experts in the field to review and provide comments on the guideline.

1.5.3 Methods for evidence synthesis

Key information sources

The WHO Guideline Steering Group formulated PICO questions (population, intervention, comparator and outcome) to guide the systematic reviews to support the development of the guideline. Scoping meetings on the treatment of HIV among adolescents *(11)* and on the use of pre-exposure prophylaxis for preventing people from acquiring HIV contributed to this process. The following three PICO questions of relevance to this guideline were identified.

- In adults, adolescents and children with HIV, is ART initiated at a threshold above CD4 500 cells/mm^3 compared with less than 500 cells/mm^3 more harmful?
- Should pregnant and breastfeeding women with HIV started on triple ARV drugs continue on lifelong ART regardless of eligibility criteria?
- Should oral PrEP containing TDF be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches?

No changes have been made to the scope of the guideline since approval of the planning proposal.

A list of potential outcomes of interest for each question was circulated to all members of the Clinical Guideline Development Group, and each member scored the importance on a scale of 1 (not important) to 9 (critical) from the perspective of individuals living with HIV. The average of the scores and variability for each outcome was used to inform the decision-making.

Systematic review teams developed protocols and conducted reviews in accordance with PRISMA reporting guidelines for systematic reviews and meta-analyses *(12)*. Annex 2 includes search strategies, quality assessment and synthesis of findings.

Qualitative literature reviews were conducted to support all three questions. To further explore acceptability, community consultations were conducted on when to start ART (Annex 2). Seven networks of people living with HIV, supported by a global research organization, conducted 24 workshops to assess the acceptability of earlier initiation of ART for people living with HIV, caregivers and service providers in eight countries (India, Indonesia, Kenya, Peru, Portugal, Ukraine, Zambia and Zimbabwe).

An additional global consultation on adolescent treatment and care and a facility-based situational analysis also contributed to the evidence base on the acceptability of earlier initiation of ART for adolescents.

Quality of evidence and strength of the recommendations

The GRADE method was used to rate the quality of the evidence *(13–21)* and determine the strength of the recommendations (Table 1) *(22)*.

The quality of evidence is defined as the confidence that the reported estimates of effect are adequate to support a specific recommendation. The GRADE system classifies the quality of evidence as high, moderate, low and very low. Randomized controlled trials are initially rated as high-quality evidence but may be downgraded for several reasons, including risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias. Observational studies are initially rated as low-quality evidence but may be upgraded if the magnitude of the treatment effect is very large, if evidence indicates a dose–response relationship or if all plausible biases would underestimate the effect.

Table 1 GRADE quality of evidence

Quality of evidence	Rationale
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

The strength of a recommendation reflects the degree of confidence of the Clinical Guideline Development Group that the desirable effects of the recommendation outweigh the undesirable effects based on the quality of the evidence. Desirable effects (potential benefits) may include beneficial health outcomes (such as reduced incidence of HIV and reduced morbidity and mortality); reduction of burden on the individual and/or health services; and potential cost savings for the individual, communities, programme and/or health system. Undesirable effects (potential harm) include those affecting individuals, families, communities or health services. Harm may include the resource use and cost implications of implementing the recommendations; adverse clinical outcomes (such as drug resistance or drug toxicity); and legal ramifications, in which certain practices are criminalized.

The strength of a recommendation can be either strong or conditional.

A strong recommendation is one for which there is confidence that the desirable effects of adherence to the recommendation clearly outweigh the undesirable effects.

A conditional recommendation is one for which the quality of evidence may be low or may apply only to specific groups or settings, or the panel concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects or are closely balanced, but the panel is not confident about these trade-offs in all situations. At implementation, monitoring and rigorous evaluation is needed to address these uncertainties, which are likely to provide new evidence that may change the calculation of the balance of trade-offs and suggest how to overcome any implementation challenges.

Clinical Guideline Development Group meeting

The Clinical Guideline Development Group met for five days in Geneva, Switzerland in June 2015. The systematic reviews and evidence to decision-making tables prepared in accordance with the GRADE process (Table 2) were presented, and the methodologist facilitated discussions. Annex 2 provides all evidence to decision-making tables, which include GRADE evidence profile tables.

Table 2 Criteria for consideration in evidence to decision-making tables

Domain	Rationale
Quality 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 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.
Costs and resource implications	How large the requirements are in resource use of the intervention and the alternative. Costs: 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 cost (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 groups 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. If there is a great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted, it is more likely that a conditional recommendation will be made.
Feasibility	Is it feasible to implement an intervention and to sustain it? If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.

The Clinical Guideline Development Group made decisions by consensus. Voting was conducted as a decision-making aid for the question of when to initiate ART for adults in relation to the strength of the recommendation (with a majority vote of 70%).

1.5.4 Peer review

A draft of the guideline was circulated for review to members of the Clinical Guideline Development Group, the Core Group and the External Review Group. The WHO Guideline Steering Group reviewed the comments and incorporated them into the final document following discussion with the technical leads.

RECOMMENDATIONS

02

2. RECOMMENDATIONS

Format of the recommendations

The recommendations are presented in the following format to reflect the review of the evidence and other considerations by the Clinical Guideline Development Group.

Recommendation. The recommendation and the strength and quality of evidence assessed using the GRADE method are stated.

Background. Previous WHO guidance in this area and key developments since recommendations were last published are described. When the recommendation relates to a specific population, key issues for that population may be briefly summarized.

Rationale and supporting evidence. New evidence on which the recommendation is based and other key operational and programmatic considerations that informed the development of the recommendation are summarized.

This includes assessments of:

- comparison of benefits and harm
- cost and cost–effectiveness
- equity and acceptability
- feasibility.

Implementation considerations. Key implementation issues specific to the recommendation are discussed.

Research gaps. Critical issues requiring further research are briefly described.

2.1 When to start antiretroviral therapy

2.1.1 When to start ART among adults (>19 years old)

NEW

Recommendation

- ART should be initiated among all adults with HIV regardless of WHO clinical stage and at any CD4 cell count *(strong recommendation, moderate-quality evidence)*.
    - As a priority, ART should be initiated among all adults with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adults with CD4 count ≤350 cells/mm^3 *(strong recommendation, moderate-quality evidence)*.

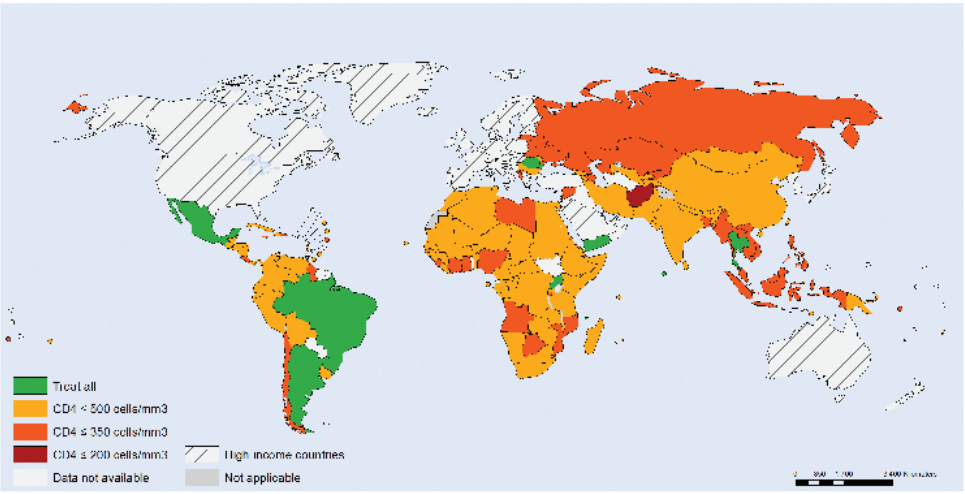
Background

Since they were first published in 2002, WHO guidelines on ART have evolved as the body of evidence to support the earlier initiation of ART has progressively grown *(1)*. The 2013 WHO consolidated ARV guidelines recommended initiating ART for all adults with HIV and a CD4 count at or below 500 cells/mm^3, regardless of WHO clinical stage, giving priority to those with severe or advanced HIV disease (WHO clinical stages 3 or 4) or a CD4 cell count at or below 350 cells/mm^3 *(2)*. This strong recommendation was based on moderate-quality evidence from three randomized controlled trials *(3–5)* and 21 observational studies *(6–27)* showing that initiating ART at or below a CD4 threshold of 500 cells/mm^3 compared with later initiation reduced the risk of progression to AIDS and/or death, TB and developing a non-AIDS-defining illness and increased the likelihood of immune recovery. In addition, high-quality evidence from one randomized controlled trial indicated that earlier ART can markedly reduce the risk of sexual transmission to HIV-negative sexual partners among heterosexual couples *(4)*.

Mathematical models and ecological studies also suggested that initiating ART earlier could affect HIV incidence at the population level if there is high uptake of sustained testing, ART coverage and retention *(28–32)*. For people with certain clinical conditions such as TB, hepatitis B (HBV) coinfection requiring HBV treatment, pregnancy, breastfeeding and HIV serodiscordant couples, the 2013 guidelines recommended initiating ART regardless of WHO clinical stage or at any CD4 cell count.

Global ART coverage for all individuals living with HIV had reached approximately 41% – or 15 million people – by March 2015 *(33)*. According to the WHO Country Intelligence Database, by June 2014, more than half (60%) of the 58 WHO HIV focus countries had adopted the CD4 threshold of 500 cells/mm^3 or less for initiating ART, and 7% *(n=4)* had already moved the CD4 threshold to above 500 cells/mm^3 (Fig. 1) *(34)*. Although the median CD4 count at the time of ART initiation is increasing, it remains significantly lower than 350 cells/mm^3 in almost all settings, including high-income countries *(35,36)*, and late presentation for treatment is associated with high early mortality rates, higher direct health-care costs and poor retention in care *(37–39)*. Increasing knowledge of HIV status, strengthening links between testing and care, modifying health systems to manage patient volumes and ensuring optimal long-term retention and adherence remain significant challenges in many settings *(40)*.

Fig. 1. Uptake of WHO policy on the threshold for initiating ART among adults and adolescents living with HIV in low- and middle-income countries, 2014



Source: Global AIDS Response Progress Reporting (WHO, UNAIDS, UNICEF)

Rationale and supporting evidence

Initiating ART among all adults living with HIV regardless of WHO clinical stage or at any CD4 cell count

Since 2013, evidence and programmatic experience have continued to favour earlier initiation of ART because of reduced mortality, morbidity and HIV transmission outcomes. Increasing evidence from systematic reviews and cohort analyses also indicates that untreated HIV infection may be associated with the development of several non-AIDS-defining conditions (including cardiovascular disease, kidney disease, liver disease, several types of cancer and neurocognitive disorders) *(41–44)* and that initiating ART earlier reduces such events and improves survival. Recent evidence from a large randomized clinical trial also shows that, as demonstrated for heterosexual serodiscordant couples, ART substantially reduces sexual transmission to HIV-negative sexual partners among homosexual couples *(45)*.

The recommendation to initiate ART at any CD4 cell count was based on a systematic review with GRADE evidence profiles that assessed the quality and strength of the evidence from one randomized controlled trial *(46)* and 17 observational studies *(11,12,15–19,23,27,30,47–52)* reporting clinical, immunological and virological outcomes and HIV transmission.

In the analysis of data from the single randomized controlled trial (TEMPRANO), moderate-quality evidence (downgraded from high quality because of imprecision) showed that initiating ART at a CD4 count >500 cells/mm^3, in the absence of other treatment indications, leads to less severe HIV morbidity (combined outcome of death, AIDS and severe non-AIDS diseases such as malignancies and bacterial diseases) compared with treatment initiation at a CD4 count at or below 500 cells/mm^3 (hazard ratio = 0.56, 95% confidence interval (CI) 0.33–0.94) *(46)*.

Limited data from another randomized clinical trial (START study) unpublished at the time of the Clinical Guideline Development Group meeting were available but not incorporated into the systematic review or GRADE table *(53)*. The Data and Safety Monitoring Board advised immediate dissemination of the findings from the START study because of predefined stopping rules. The START trial was not part of the systematic review because the comparison groups did not match the review PICO and was therefore not considered in relation to the quality of the evidence. Box 1 summarizes the key findings from the START study that were presented to the Clinical Guideline Development Group and are supportive of the new recommendation.

Analysis of the observational studies found a significantly lower risk of HIV disease progression *(50)*, and the TEMPRANO randomized controlled trial data demonstrated from modelling the potential lower rates of HIV transmission to uninfected partners *(46)*, but the evidence was rated as very low quality in both cases. However, interim data from the HPTN 052 clinical trial indicated that early ART is highly effective at prevention of sexual transmission of HIV *(54)*. Similar to the START trial, relevant data from the HPTN 052 were unpublished at the time of the guidelines review meeting and were not incorporated into the systematic review due to a different comparator to that of the review. Box 2 summarizes these data.

Box 1. The START study

The Strategic Timing of Antiretroviral Treatment (START) trial enrolled 4685 people at 215 sites in 35 countries. Twenty-seven percent of the participants were women, and approximately half were gay men. The study examined the rates of AIDS and serious AIDS-defining illness or death among people who were randomized to receive immediate ART versus deferring ART until their CD4 count dropped below 350 cells/mm^3. The median baseline CD4 count was 651 cells/mm^3 in the intervention group. In the deferred group, the median CD4 count at ART initiation was 408 cells/mm^3. Follow-up lasted for a mean of three years. A total of 86 events (death, AIDS and serious non-AIDS events) occurred among those with later treatment initiation, whereas 41 events occurred among those starting ART immediately, representing a 57% reduction in negative outcomes among those treated early. In both groups, most events occurred when CD4 counts were higher than 500 cells/mm^3. The study also showed that immediate ART reduced both AIDS-related and non-AIDS-related events, but the benefit was greater for AIDS-related events. Tuberculosis (TB), Kaposi sarcoma and lymphoma — the most common AIDS-related events — all occurred less frequently in the immediate ART group. Cancer rates (combining AIDS and non-AIDS malignancies) were lower in the immediate ART group, but cardiovascular disease rates were similar between groups. These effects were consistent in countries of different income levels and across geographical regions.

Box 2. New data from HPTN 052

The HIV Prevention Trials Network (HPTN) 052 study showed that starting ART early reduced the overall risk of HIV sexual transmission to uninfected partners by 93% *(54)*. In this Phase 3 randomized controlled trial, 1763 HIV serodiscordant couples from 13 sites in 9 countries (97% of whom were heterosexual couples) were enrolled and followed for approximately four years. The participating couples were randomly assigned to one of two treatment groups. In the first group, the participants living with HIV began ART immediately. In the second group, the participants living with HIV delayed treatment until their CD4 counts fell below 250 cells/mm^3 or they were diagnosed with an AIDS-related illness. All participants in both groups received counselling on safe sex practices, free condoms, treatment for sexually transmitted infections, frequent HIV testing and evaluation and treatment for any complications related to HIV. The median CD4 count at study entry was 436 cells/mm^3. The HIV-uninfected partners tested negative for the virus within 14 days of entering the study. In the overall analysis, from April 2005 through to May 2015, the investigators found that 78 initially negative partners became infected with HIV, and 46 of 70 cases where linkage status was confirmed (66%) of these partners acquiring HIV could be linked to the positive partner using phylogenetic analysis.

Three of the 46 linked infections occurred in the early ART arm and 43 in the delayed ART arm, leading to a 93% risk reduction for linked transmission. In the final analysis, all linked partner infections that were diagnosed after ART began are likely to have occurred when the virus was not suppressed by the treatment regimen (4 of 8 cases). The investigators did not observe any linked partner infections when the HIV-infected participant's virus was stably suppressed by ART. The results indicate that ART is highly effective at preventing the heterosexual transmission of HIV if viral suppression is achieved and maintained.

Moderate-quality evidence from the TEMPRANO trial showed that initiating ART at a CD4 count above 500 cells/mm^3 was not associated with increased risk of grade 3 or 4 adverse events[2] *(46)*. Low-quality evidence from observational data showed an increased risk of any severe laboratory adverse event and hepatic adverse events in individuals initiating ART at CD4 count above 500 cells/mm^3, although this was not associated with treatment discontinuation *(48)*.

Programmatic data from several countries that are offering earlier ART either to all people living with HIV or to specific populations have shown significant increases in ART uptake and linkage to care, reduction in the time between HIV diagnosis and ART initiation regardless of baseline CD4 cell count and an increase in the median CD4 value at ART initiation. Retention in care has not differed between individuals who start at CD4 counts above 500 cells/mm^3 compared with those who started based on the standard of care *(55–57)*.

Initiating ART among adults with severe or advanced HIV disease or with CD4 count at or below 350 cells/mm^3 as a priority

The benefits of initiating ART are greatest among individuals with symptomatic HIV disease or those with lower CD4 counts. The strength and quality of evidence for this recommendation established in the 2010 ART guidelines *(58)* remains unchanged. Moderate-quality evidence from two randomized controlled trials and several observational studies show that initiating ART at CD4 counts at or below 350 cells/mm^3 significantly reduces mortality, disease progression and the incidence of opportunistic diseases, especially TB and non-AIDS-defining conditions *(59)*. Further, several studies and programmatic data suggest that late diagnosis (often defined as CD4 count at or below 350 cells/mm^3) and late treatment initiation are very common, even in high-income settings *(60,61)*.

Comparing benefits and harm

The benefits of earlier ART initiation include fewer events of severe HIV morbidity and disease progression, improved uptake and initial linkage to care, better immune recovery and decreased HIV transmission. However, not all observational studies have consistently demonstrated the beneficial effect of initiating ART at CD4 cell count at or above 500 cells/mm^3 on mortality, the incidence of inflammation-related non-AIDS events and ongoing viral replication compared with initiation at CD4 at or below 500 cells/mm^3. Follow-up will be needed to evaluate the potential harm and benefits of ART over a lifetime.

It is increasingly recognized that, in settings with a high burden of HIV and TB infections, increasing ART coverage is associated with decreasing TB case notifications, and this is likely to improve when ART is started earlier.

A modelling exercise based on national cohort data from four countries in sub-Saharan Africa concluded that programmatic gains and mortality reduction were accrued by eliminating the pre-ART period, suggesting that making treatment available to everyone will strengthen the continuum of care *(62)*.

Cost and cost–effectiveness

The same modelling exercise indicates that expanding ART eligibility criteria to above 500 cells/mm^3 or regardless of CD4 cell count and linking to HIV care could result in 6–14% fewer people dying from HIV-related causes during the next decade *(62)*. In this exercise, the vast majority of the impact is caused by programmatic simplification leading to more people initiating ART in a timely manner and therefore avoiding adverse outcomes during the per-ART period rather any

[2] Grade 3 and 4 adverse events are clinical and laboratory abnormalities usually requiring discontinuation of ARV drugs until the person is stabilized and an alternative drug can be used.

direct therapeutic benefits. The increased cost of earlier ART would be partly offset by subsequent reduced costs (such as decreased hospitalization and increased productivity) and preventing people from acquiring HIV infection. The modelling results suggest that such a change is likely to be cost-effective in many settings if people initiating ART adhere to treatment and retention in care is maintained. Costs will increase significantly but far less than if the additional outreach interventions required to maintain individuals in pre-ART care are also included.

According to UNAIDS estimates, expanding ART to all people living with HIV is projected to avert 21 million AIDS-related deaths and 28 million new infections by 2030 *(63)*. However, these benefits require high testing uptake, high treatment coverage, sustained adherence and high rates of retention in care. The cost implications at the regional and country levels can also vary and should be further explored, since countries have different levels of current treatment coverage and local cost considerations depending on their context and resources.

Equity and acceptability

Concerns have been expressed that, given limited resources, very early treatment could result in some people who urgently need treatment being displaced by people for whom treatment would be beneficial but is less urgently needed. For this reason, initiating ART among adults with severe or advanced HIV disease or with a CD4 count at or below 350 cells/mm^3 is recommended as a priority in this guideline. Additional concerns that mandatory or coercive approaches will be used among high-risk marginalized populations highlight the importance of adequate patient information, informed consent, appropriate health worker training and rights-based legal frameworks to facilitate access.

The community-led global consultation examining the acceptability of earlier initiation of ART at a higher CD4 count for people living with HIV, caregivers and service providers found that earlier initiation was considered acceptable. Participants in the consultation emphasized the need for collaborative decision-making with service providers to ensure that the ultimate decision to initiate ART rests with the person living with HIV. Motivation to start and adhere to treatment may be more difficult for people who feel well and have higher CD4 counts than for people who are or have been ill. Stigma and discrimination continue to act as barriers to treatment access and adherence. Critical factors in promoting ongoing engagement in care and adherence include ensuring access to a stable supply of free or affordable ARV drugs, facilities that are easily accessible and that ensure confidentiality, sympathetic providers and community adherence support.

A qualitative literature review showed that acceptability for earlier treatment is greater when people know that treatment reduces mortality risk. Service providers recognize the preventive benefits of earlier ART and the need for earlier ART initiation for asymptomatic people. Among people living with HIV, acceptance increases when they also have comorbidities or conditions associated with a higher risk of HIV transmission. Issues cited in the literature supported those identified in community consultations.

Feasibility

According to cohort and national programme data, the number of people needing treatment could increase by up to 35% if ART is initiated at any CD4 count rather than at or below 500 cells/mm^3 *(63)*. Modelling estimates predict that this increase would be lower, in the range of 7% to 21% over five years, because not all people living with HIV are diagnosed and present for care immediately. Country experience has also shown that moving to a higher CD4 threshold for ART initiation may not necessarily lead to a significant immediate increase in the numbers of people who actually access treatment in the absence of increased uptake of HIV testing, stronger linkage to care, adequate treatment monitoring and sustained adherence support. Late presentation for treatment is still quite common, with the median CD4 count at ART initiation below 350 cells/mm^3 in the majority of settings, including high-income countries (*59,60*).

Implementation considerations

Regardless of the epidemic profile and disease burden, priority should be given to people with symptomatic HIV disease or with CD4 count at or below 350 cells/mm^3 who are at high risk of mortality and most likely to benefit from ART in the short term.

Initiating ART at CD4 counts above 500 cells/mm^3 may involve additional human, infrastructure and financial resources. Countries vary in health system capacity and are at different stages in ART coverage and quality of care. A phased approach to implementation may be needed, especially in settings with a high burden of HIV infection, lower ART coverage, less developed health systems, lower rates of testing, poor pre-ART care, weaker human resources, limited laboratory capacity, budget constraints and/or competing health priorities. In such settings, equity considerations and giving priority to those who most need treatment should guide implementation. The updated consolidated guidelines will provide further guidance in this area.

The increased need for ART associated with early initiation may place demands on the health system in some settings that could increase the risk of drug resistance, such as drug stock-outs, insufficient patient preparation and suboptimal adherence. To maximize the long-term effectiveness of first-line ART regimens and ensure that people are taking the most effective regimen, the scaling up of HIV treatment should be accompanied by measures to monitor and improve service quality at the site and programme levels.

In all settings, continued monitoring of the long-term safety profile of ARV drugs and the implications of earlier initiation for drug resistance, toxicity and adherence will be needed. It also remains essential to address structural and social barriers to accessing treatment faced by key populations, such as criminalization, discrimination and stigma *(64–66)*.

Research gaps

Several ongoing implementation trials are evaluating the feasibility, acceptability, cost–effectiveness and impact of immediate treatment for all people living with HIV regardless of CD4 cell count at the population level (SEARCH and MaxART studies). Primary outcome results are not expected before 2017 or 2018 *(67,68)*. Three large randomized trials are examining the population effect of early ART initiation on HIV incidence and mortality (Botswana Combination Prevention Trial, HPTN-071 (PopART) study and 12249 ANRS TasP trial), with results expected in 2018 or 2019 *(69–71)*.

Other research priorities include assessing the incidence of short- and long-term severe adverse events as a result of increased exposure to ART, barriers to and enablers of adherence and long-term retention in care and the impact on the cascade of care and the magnitude of the prevention benefit of early initiation of ART, especially among key populations and adolescents.

2.1.2 When to start ART among pregnant and breastfeeding women

UPDATED

Recommendation

ART should be initiated in all pregnant and breastfeeding women living with HIV regardless of WHO clinical stage and at any CD4 cell count and continued lifelong *(strong recommendation, moderate-quality evidence)*.

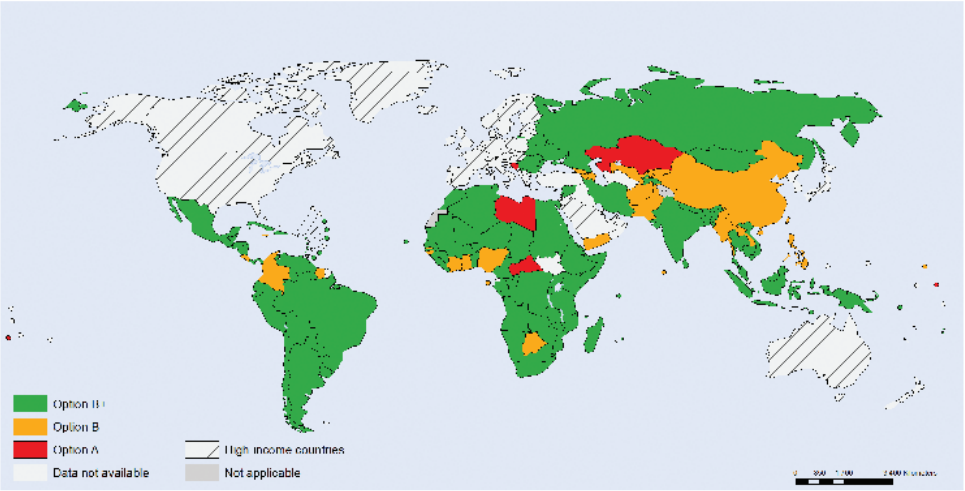
Background

Programmes to prevent mother-to-child transmission were some of the earliest public health interventions that used ARV drugs to reduce the risk of HIV transmission. Initially, the regimen recommended by WHO was a single dose of nevirapine given to the mother during labour and to the infant in the first few days of life. With the launch of the "3 by 5" initiative and the rolling out of national HIV care and treatment programmes, the guidelines made an important shift, recommending that pregnant women should be tested for HIV and then assessed for treatment eligibility. Those considered eligible for treatment should be offered combination lifelong antiretroviral therapy for their own health, while those who were not eligible should receive short courses of antiretroviral prophylaxis for PMTCT. Although eligibility criteria have changed and the preferred regimens for ART and for PMTCT prophylaxis have evolved, this distinction between treatment and prophylaxis became a fixture of PMTCT programmes.

In 2013, the consolidated ARV guidelines recommended that all pregnant and breastfeeding women be initiated on ART regardless of clinical eligibility. This recommendation was driven by practical experience from programmes showing that PMTCT prophylaxis (using different drugs at different times in the course of pregnancy, labour and delivery as well as long duration of infant prophylaxis while breastfeeding) was more challenging to implement in the field than giving ART to all pregnant women (especially if the ART regimen was a once-daily fixed-dose combination tablet). However, the guidelines still offered programmes the option to either continue ART lifelong in all women (option B+) or to stop ART after the period of mother-to-child transmission risk in women who did not otherwise meet eligibility criteria (option B). Option B+ was felt to be of the greatest benefit in settings with high HIV prevalence and high fertility in which initiating ART among all pregnant and breastfeeding women would reduce HIV incidence and prevent HIV transmission in both current and future pregnancies.

Following the release of the 2013 guidelines, many countries moved to adopt option B+ as the preferred approach for PMTCT programmes. The most recent Global AIDS Response Progress Reporting data show that the majority of countries, including almost all the 22 high-priority countries listed in the Global Plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive *(72)*, are now either piloting or implementing lifelong ART for all pregnant and breastfeeding women living with HIV at a national scale (Fig. 2).

Fig. 2. Adoption of policy on preventing the mother-to-child transmission of HIV in low- and middle-income countries, 2014



Source: Global AIDS Response Progress Reporting (WHO, UNAIDS, UNICEF)

Increasing evidence to support earlier ART initiation among all adults as described in the previous section, as well as widespread uptake of option B+ and emerging programme data on the success of option B+ in practice, all support a revised recommendation in 2015 that all pregnant and breastfeeding women living with HIV should initiate ART and remain on lifelong treatment regardless of clinical or CD4 stage of disease. As a result, option B is no longer relevant.

Providing ART to all pregnant and breastfeeding women living with HIV serves three synergistic purposes: (1) improving individual health outcomes, (2) preventing mother-to-child transmission of HIV and (3) preventing the horizontal transmission of HIV from the mother to an uninfected sexual partner.

Rationale and supporting evidence

The evidence on options B and B+ and the clinical and immunological impact of stopping ART among postpartum women were reviewed in the context of increasing data showing the benefit of ART at all stages of HIV disease and the strong, new recommendation to initiate ART among all adults with HIV at any CD4 count.

A systematic review was conducted to compare option B and option B+ in terms of maternal health outcomes. The review did not identify any randomized controlled trials or observational studies that directly compared options B and B+; however, 18 studies reported on option B outcomes – comprising four randomized controlled trials *(73–76)*, three single-arm trials *(77–79)* and 11 cohort studies *(80–90)* – and 10 cohort studies reported on outcomes associated with option B+ *(91–100)*. All the studies evaluating option B+ suggested that women experienced health benefits in terms of immunological and clinical parameters. None of the studies included in the review reported on how option B+ affected HIV transmission rates to partners, although this is an important likely benefit for women who remain on lifelong ART.

Since the key difference between option B and option B+ is not when ART is started but whether it is stopped, literature on the clinical and immunological impact of stopping ART among women during the postpartum period was also reviewed. Five cohort studies and one randomized controlled trial were identified that examined changes in clinical and immunological parameters following discontinuation of ARV drugs. Most of these studies used the historical threshold for ART initiation of CD4 count below 350 cells/mm^3, and in several cases mothers were receiving ARV prophylaxis rather than ART, but all showed a gradual decline in immune function after ARV drugs were stopped. Using the time frame of six months after discontinuation, 6–20% of women with a baseline CD4 count below 500 cells/mm^3 had become eligible, whereas only 1.5% of women became eligible if the baseline CD4 was above 500 cells/mm^3 *(101,102)*. A lower baseline CD4 count was also associated with a 2.5-fold higher risk of WHO stage 2 or 3 clinical events *(103)*.

Apart from the impact on clinical and immunological outcome, there are also programmatic consequences of stopping ARV drugs among postpartum women. In one study from Malawi, loss to follow-up post-delivery was much higher in women with baseline CD4 above 350 cells/mm^3 (who were not eligible for treatment) than those with CD4 below 350 cells/mm^3 (who were eligible and started on ART) *(104)*. The findings were similar in a South African cohort where the women who were considered ineligible for ART were twice as likely to be lost to follow-up at six months postpartum as the women who had started treatment *(105)*.

The body of evidence demonstrates the advantages of lifelong ART for pregnant and breastfeeding women and adds to the compelling data from recent randomized clinical trials suggesting that all adults with HIV benefit from ART at any CD4 and regardless of their clinical stage of disease.

Comparing benefits and harm

Most countries are moving to adopt universal ART for all pregnant and breastfeeding women. The benefits include improved health outcomes, lower mortality and the potential for reduction of horizontal transmission of HIV. Women may be less likely to drop out of care after the end of the transmission risk period and may avoid some of the clinical and operational complexity of repeated cycles of stopping and starting ART in subsequent pregnancies.

The risks to offering lifelong ART to all pregnant and breastfeeding women living with HIV as opposed to ART only during the period of mother-to-child transmission risk include the potential for cumulative drug toxicity and the possibility of poor adherence with long-term use, potentially leading to the development of drug resistance. In general, these risks for pregnant and breastfeeding women are similar to those for non-pregnant adults. A further potential risk to the fetus may arise from exposure to ARV drugs, especially when given early in the gestational period. Early gestation exposure is more likely with the change in guidelines for adults, as a greater number of women of childbearing age will initiate ART across all CD4 counts. To date, no evidence suggests a significant increased risk of congenital anomalies associated with the currently recommended first-line ARV drug regimens *(106)*. How the recommendations are implemented may also affect outcomes.

The costs associated with implementing option B+ will probably require increased resources, especially in the short term. Nevertheless, overall, the benefits of option B+ are considered to outweigh the potential harm.

Cost and cost–effectiveness

In a cost-modelling exercise, the total cost (including drugs, diagnostics and service delivery) of keeping a woman on option B+ was an estimated US$ 2069 over five years *(107)*. However, since maintaining a woman off ART also incurs costs for monitoring and follow-up, the incremental cost of moving from option B to option B+ was relatively low and varied between US$ 92 and US$ 605 depending on baseline CD4 and breastfeeding status. Several model-based analyses have supported the cost–effectiveness of strategies for preventing the mother-to-child transmission of HIV, with many finding option B and B+ to be cost-saving or highly cost-effective compared with option A. When outcomes beyond the mother-to-child transmission of HIV are considered, such as maternal health, preventing the mother-to-child transmission of HIV in future pregnancies and preventing horizontal transmission, option B+ has been found to be highly cost-effective compared with option B *(108,109)*.

Equity and acceptability

A qualitative literature review on the acceptability of option B+ indicated high acceptability of lifelong ART among pregnant and breastfeeding women as well as among service providers. Women have raised some concerns about fear of drug toxicity for themselves and their children, but women generally value the health benefits and the ability to protect their children and their partners from HIV *(110,111)*. The review also highlighted some of the challenges of lifelong treatment, including disclosure to partners and employers, stigma, lack of support and costs and time off work associated with clinic visits and drug pick-ups.

Early programme experience from South Africa suggests that pregnant women find same-day initiation of ART (starting ART on the day of HIV diagnosis) acceptable, especially because in this setting, many women are already aware of their status, have high levels of treatment literacy and can access support services *(112)*. By contrast, same-day ART initiation in Malawi has been

associated with a high rate of early loss to follow-up, with many women failing to return for a second visit *(113)*.

The recommendation to initiate ART for all adults with HIV at any CD4 count will likely add to the acceptability of ART for pregnant and breastfeeding women, since it normalizes what may previously have been considered stigmatizing. A simplified and harmonized approach to ART among pregnant and non-pregnant adults will also promote health equity.

Implementation considerations

Many of the concerns raised about the recommendation to give all pregnant and breastfeeding women lifelong ART relate to how this policy should be implemented. Programme managers must address the issues of ensuring the quality of HIV testing, determining when to initiate ART in a newly diagnosed woman and maintaining the continuity of ART services in the postpartum period when implementing this recommendation.

ART for pregnant and breastfeeding women should ideally be delivered within maternal, newborn and child health clinics by integrating HIV and antenatal care. Integrated services benefit mothers, and this is likely to be feasible in settings with a high burden of HIV infection. However, achieving integration will depend on the context and the resources available in terms of staff time and physical space. In one retrospective cohort study from Malawi, 45% of the women interviewed reported that, although they started ART in an antenatal care clinic, they were referred to separate ART services soon after delivery *(114)*. There is no established model for when to transition mothers on ART out of maternal, newborn and child health services, but a recent report from South Africa highlighted the importance of this potential additional loss point in the PMTCT cascade. In a retrospective review of women referred to ART clinics in the postpartum period, up to 25% did not remain in care five months after referral *(115)*.

Beyond issues related to clinical service delivery, a key consideration for national programmes is the need for strengthened data systems to track women on ART across multiple delivery sites, along with the need for targeted interventions to improve adherence and retention, such as community support and the use of peer counsellors.

Research gaps

Significant knowledge gaps remain about where and how best to implement option B+ to improve retention and follow-up of the mother and infant pair. For example, the integration of ARV drug delivery in antenatal care and maternal, neonatal and childcare services as opposed to referral to ART clinics requires further implementation and assessment.

Adolescents and young women living with HIV face unique challenges in preventing the transmission of HIV to their children and attending to their own health needs, including poor access to reproductive health services, poor uptake of testing and poor retention in care *(116)*. Operational research is urgently needed to identify the drivers of poor outcomes among adolescents, to define how to provide adolescent-friendly maternal and newborn health services and to develop specific strategies to improve retention in care.

Although ART in pregnancy and during breastfeeding provides clear public health benefit in terms of maternal health and PMTCT, the potential long-term harm from fetal and infant exposure to maternal drugs is poorly understood. The risk of congenital birth defects is likely to be low for the currently recommended first-line ARV drugs, but little is known about newer drugs and the possible effects on growth, development and organ maturation resulting from exposure to ART absorbed across the placenta and through breast-milk.

2.1.3 When to start ART among adolescents (10–19 years of age)

Recommendation

NEW

- ART should be initiated among all adolescents living with HIV regardless of WHO clinical stage and at any CD4 cell count *(conditional recommendation, low-quality evidence)*.
    - As a priority, ART should be initiated among all adolescents with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and adolescents with CD4 count ≤350 cells/mm^3 *(strong recommendation, moderate-quality evidence)*.

The review of evidence, programmatic data, operational considerations and values and preferences expressed by young people living with HIV led to the development of a separate recommendation for adolescents. This highlights the important considerations of initiating ART and providing treatment and care for adolescents living with HIV.

An estimated 2.1 million adolescents (10–19 years old) globally were living with HIV in 2013. HIV-related deaths among adolescents are estimated to have tripled since 2000, making HIV the second leading cause of death among adolescents worldwide *(117)*.

Adolescence is marked by rapid physical, neurodevelopmental, emotional and social changes *(118)*. Although data are lacking on HIV mortality in the age group 5–14 years old, adolescents appear to be underserved by current HIV services, have significantly worse access to and coverage of ART than adults, have high risk of loss to follow-up *(119–121)* and have suboptimal adherence and special requirements for comprehensive care, including psychosocial support and sexual and reproductive health care *(122–124)*. Adolescents also face significant barriers to accessing the essential health and support services they need, especially because of policy and legal barriers related to the age of consent *(125)*.

The 2013 WHO consolidated ARV guidelines aligned the clinical and immunological criteria for ART eligibility among adolescents with those for adults (treatment initiation for WHO clinical stage 3 or 4 disease or at a CD4 count at or below 500 cells/mm^3) with the aim of enhancing programmatic simplicity and avoiding delays in treatment initiation while assessing eligibility.

Rationale and supporting evidence

The recommendation is also based on the strong operational and programmatic advantages of alignment with the criteria for initiating ART among adults and children and the clinical benefits demonstrated by evidence from adult studies *(126)*.

A systematic review of the evidence did not identify any study investigating treatment initiation strategies specific to adolescents. This subgroup was also not captured by adult studies that assessed the clinical outcomes of immediate versus CD4-driven ART initiation *(127,128)*.

Perinatally infected adolescents are more likely to experience chronic diseases and neurodevelopmental, growth and pubertal delays in comparison to their age-matched peers. Older adolescents who acquire HIV behaviourally do not present the same clinical features but face potentially greater challenges in dealing with stigma and lack of family and community support to access care.

There are some limitations in extrapolating from the evidence for adults and some uncertainty around the potential benefits that immediate initiation of ART may have on adolescent health outcomes given the unique challenges that may arise in achieving long-term adherence and retention among adolescents. For this reason, the quality of the evidence reviewed for adults was downgraded for indirectness, and the overall quality of the evidence for treating all adolescents living with HIV was rated as low.

Comparing benefits and harm

To assess the potential benefits of starting ART earlier, a causal modelling study of data from southern and western Africa and Europe was updated using prospective data. This examined 4553 ART-naive perinatally infected adolescents 10–15 years old (median age 12.4 years), of whom 14% presented with CD4 counts above the existing eligibility thresholds of 500 cells/mm^3. In the analysis, median follow-up time was 656 days. Mortality appeared higher when ART was started very late. However, after four years of follow-up, the difference between immediate ART versus initiating ART at or below 500 cells/mm^3 was insignificant. These differences were similar for the adolescents who presented with a CD4 count above 500 cells/mm^3. Overall, the study did not show any clear survival or growth benefit from early treatment in this population *(129)*.

Indirect evidence showed that perinatally infected adolescents for whom treatment initiation is delayed to 10 years of age are unlikely to normalize CD4 count *(130)* and, after onset of chronic lung disease, do not fully recover lung functioning *(131)*, suggesting that adolescents who have survived through childhood untreated may have limited gains from initiating ART earlier compared with younger children.

The high risk of loss to follow-up in this age group, particularly among adolescents aged 15–19 years *(132–136)*, is an important factor in assessing the trade-off between risks and benefits of earlier ART initiation. Adolescents are also known to be less adherent than adults and younger children *(137)*. Two systematic reviews on adherence and viral suppression showed varying rates for adolescents *(138,139)*, and treatment failure was observed among 10% of 1007 perinatally infected children in the COHERE cohort, with the risk being higher with a longer time on ART and when treatment was started in adolescence *(140)*.

Despite the limited clinical evidence in support of earlier treatment initiation for both perinatally and behaviourally infected adolescents and potential concerns attached to the risk of drug resistance because of poor adherence, experience to date suggests that aligning with the initiation criteria for adults will contribute to simplifying programming and further expanding ART coverage *(141)* and present crucial opportunities to engage adolescents living with HIV in care.

Equity and acceptability

In community consultations, adolescents, service providers, parents and caregivers emphasized the importance of ensuring that priority be given to adolescents most in need of treatment as well as the challenge of adherence *(142–145)*. The key challenges identified included forgetting to take medicines, having unstable lives not conducive to daily medication and relative lack of power in treatment decision-making. Effective interventions and services to support adherence among adolescents – including community interventions and the use of peer educators – are required.

Feasibility and resource use

Earlier initiation of ART among adolescents is likely to be feasible within existing health systems. Because of late diagnosis *(146)*, many adolescents are already likely to be eligible based on 2013 initiation criteria, and the increase in the overall number of adolescents starting treatment would therefore be relatively small *(141)*. Increased patient enrolments would nevertheless increase demands on supply chains and provider workload. The experience of some national programmes has shown that, although all adolescents 10–15 years old can be treated, challenges include ensuring that commodities are available, strengthening laboratory systems and conducting provider training *(141)*.

Increased demand for commodities, human resources and infrastructure is expected to require additional funding. A costing analysis shows that ARV drugs are likely to be the most significant cost driver *(147)*. Laboratory commodities are likely to be the second largest contributor to total cost, followed by human resources and co-trimoxazole.

Implementation considerations

Ensuring that adolescents are diagnosed and receive ART in a timely manner will require developing adolescent-friendly health services and providers and strongly emphasizing support for adherence and retention in care. The full update of the consolidated guidelines will contain further guidance on operational and service delivery approaches to support the implementation of adolescent-friendly health services.

Research gaps

How earlier ART affects retention, adherence and HIV drug resistance among adolescents with less advanced disease requires further investigation. Improved age disaggregation of existing cohort and surveillance data is needed to improve understanding of adolescent-specific issues and needs.

2.1.4 When to start ART among children (younger than 10 years of age)

Recommendation

NEW

ART should be initiated among all children living with HIV, regardless of WHO clinical stage or at any CD4 cell count.

- Infants diagnosed in the first year of life *(strong recommendation, moderate-quality evidence)*.
- Children living with HIV one year old to less than 10 years old *(conditional recommendation, low-quality evidence)*.

As a priority, ART should be initiated among all children ≤2 years old or with WHO stage 3 or 4 or CD4 count ≤750 cells/mm³ or CD percentage <25% among children younger than 5 years and CD4 count ≤350 cells/mm³ among children 5 years and older.

Background

A review of evidence, together with programmatic data and operational considerations, has led to revised recommendations in 2015 to initiate ART in all children with HIV, aligning the recommendation for children with the new recommendations for adults and adolescents.

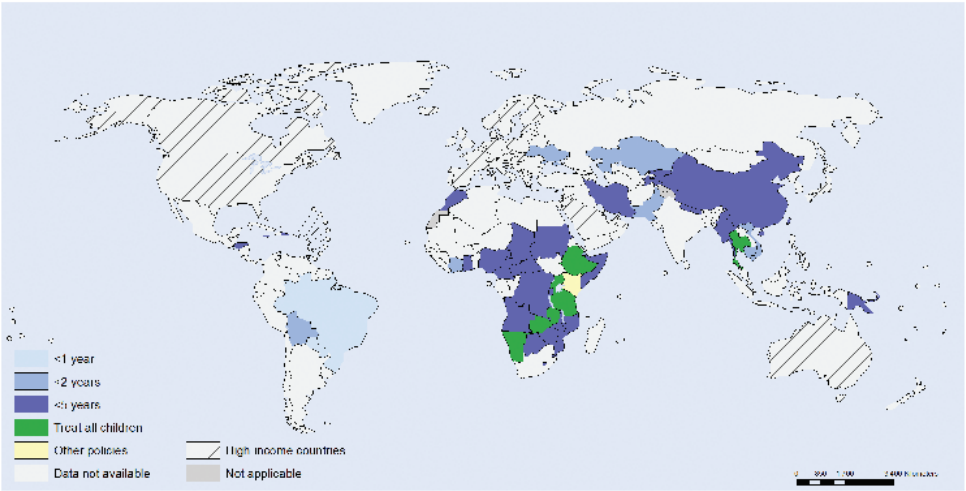
Infants and young children living with HIV have an exceptionally high risk of poor outcomes, with up to 52% of children born living with HIV dying before the age of two years in the absence of any intervention *(148)*. By five years of age, the risk of mortality and disease progression in the absence of treatment falls to rates similar to those of young adults *(149,150)*. Improved access to early infant diagnosis has increased the identification of infants living with HIV, but rates of ART initiation among infants living with HIV – all of whom should initiate treatment – remain suboptimal. Overall, most children who are eligible for ART are still not being treated, and ART coverage among children lags significantly behind that among adults: 32% versus 40% globally in 2014 *(151)*.

Diagnosing and retaining children exposed to and living with HIV in care present unique challenges because of their dependence on a caregiver. Loss to follow-up has been particularly high *(152)*, with retention especially challenging for children who are in HIV care but not receiving ART *(153)*.

The 2013 WHO ARV guidelines aligned clinical and immunological criteria for ART eligibility for children older than five years with those for adults: that is, treatment was recommended for WHO clinical stage 3 or 4 disease or CD4 counts at or below 500 cells/mm³. ART was also recommended for all children living with HIV younger than five years of age regardless of clinical or immunological status. For children between one and five years of age, it was recommended that those younger than two years of age with WHO stage 3 or 4 clinical disease or CD4 percentage below 25% or CD4 count below 750 cells/mm³ be given priority. For infants younger than one year of age, a strong recommendation to treat regardless of clinical and immunological conditions was maintained. The 2013 guidelines recognized the challenges of treating infants in their first two weeks of life because of lack of treatment options for which safe and effective dosing has been established and the lack of experience globally, further complicated by the high rates of prematurity and low birth weight in low- and middle-income countries.

Countries with a high burden of HIV among children have rapidly adopted the 2013 treatment criteria *(154)*, and some countries have decided to expand ART to all children and adolescents younger than 15 years to simplify ART delivery *(155)*.

Fig. 3. Adoption of ART initiation for infants and children in low- and middle-income countries from the Global AIDS Response Progress Reporting, 2014



Source: Global AIDS Response Progress Reporting (WHO, UNAIDS, UNICEF)

Rationale and supporting evidence

A systematic review *(127)* conducted in 2013 and updated in 2015 identified only one randomized clinical trial, PREDICT, that assessed the clinical benefit of early ART initiation among children *(156)*. The trial enrolled 300 children (1–12 years old, median age 6.4 years) with CD4 percentage above 15% and without United States Centers for Disease Control and Prevention stage C disease, randomizing them to either early treatment or deferred treatment until the CD4 percentage fell below 15%. There was no difference in AIDS-free survival or neurodevelopmental outcomes between the two arms, but height gain was better among those initiating ART earlier *(157)*.

A causal modelling study *(158)*, also updated in 2015 using prospective data, assessed outcomes for 7358 ART-naive children 5–10 years old (median age 7.2 years), of whom 26% (1903) presented with CD4 counts exceeding the existing eligibility threshold of 500 cells/mm^3. In this analysis, after five years of follow-up, early ART differed slightly but significantly in mortality from waiting for the CD4 count to fall below 500 cells/mm^3. The causal modelling analysis also showed significantly better growth response among those starting ART immediately *(159)*.

In addition, other evidence suggests that initiating ART earlier could mitigate the negative effects of HIV infection on growth and pubertal and nervous system development *(160–166)*.

Earlier ART may also promote immune recovery. In a study of the long-term effects of ART on CD4 cell evolution in children receiving ART, children with a greater degree of immunosuppression at baseline did not recover to normal values (CD4% >25%) even after five years of ART, whereas the CD4 percentage among children starting ART at higher CD4 levels normalized within a year of receiving ART *(167)*. As shown by the normalization of inflammatory markers, earlier ART initiation is also likely to reduce HIV-induced chronic immune activation, thus potentially limiting the onset of chronic lung disease and increased risk of cardiovascular disease for which clinical correlates are still missing among children *(168)*.

The recommendation to start ART immediately is conditional for children living with HIV from 1 to less than 10 years old because of the paucity of evidence supporting ART initiation regardless of the clinical and immunological conditions in this population *(160,161)*. However, this approach is expected to provide significant programmatic advantages, especially in settings with limited access to immunological testing, a high burden of HIV disease and low ART coverage among children.

Comparing benefits and harm

In addition to clinical considerations, earlier ART is likely to expand coverage in this age group. A rapid assessment conducted in May 2015 to assess the implementation of a policy to treat all children younger than 15 years in Uganda found a 74% increase in the number of children newly initiating ART and an increase in ART coverage among children from 22% to 32% between 2013 and 2014 *(141)*. The proportion of children receiving ART at lower-level health facilities increased from 42% to 46%, suggesting that simplifying the criteria for initiating treatment could also be instrumental in effectively decentralizing ART services. In addition, the time from eligibility to ART initiation significantly decreased, suggesting that simpler initiation criteria allowed more rapid treatment initiation. Programmatic experience suggests that children receiving ART have better retention than those in care but not receiving ART *(155)*. The retention rates in Uganda appeared to be comparable among children starting ART when eligible or with CD4 above 500 cells/mm^3, but there was a reduction in retention at six months, highlighting the need to ensure that children and caregivers receive appropriate counselling and support to stay in care.

The potential harm of earlier ART initiation includes short-term side effects that may predispose children to suboptimal ART adherence and subsequently treatment failure *(169,170)*, along with the emergence of drug resistance and the need for second- and third-line regimens, for which options suitable for children are still limited. Treatment failure was observed in 10% of cases in the COHERE cohort, with the risk being higher the longer children are on ART and the older they are when initiating ART *(171)*.

Increasing demands on the health system, drug stock-outs and consequent treatment discontinuation may also contribute to treatment failure and HIV drug resistance. Long-term side effects and chronic disease may result in increased morbidity and affect quality of life in adulthood. On balance, the likely clinical and programmatic benefits of earlier ART are likely to outweigh these potential types of harm.

Equity and acceptability

Expanding ART to every child living with HIV is expected to increase equity and be well accepted. In community consultations, the acceptability of earlier treatment of children living with HIV from the perspectives of parents, caregivers and health-care providers was based on the perceived health benefits for the child. However, psychosocial support for parents and caregivers, especially for disclosure, was highlighted as critical to facilitating initiation and improving adherence *(172)*.

Feasibility and resource use

Implementing this recommendation is likely to be feasible, since it represents a relatively small increased burden on current health systems *(141)*. Late diagnosis is still common *(173)*, and an estimated 80% or more of children identified as living with HIV would already be eligible for ART based on 2013 recommendations. However, increased numbers of children receiving ART may also lead to higher demand on supply chain systems and increased provider workload. Laboratory monitoring will need to be strengthened to monitor treatment efficacy and identify treatment

failures among children. The experience of some national programmes has demonstrated that treating all children with HIV is feasible but also highlights the importance of secure commodity supplies, adequate health worker training and the need to ensure sustainability of resources *(141)*.

Increased demand for HIV commodities, human resources and infrastructure may require increased funding. A costing analysis in Zambia has shown that ARV drugs are likely to be the most significant cost driver, accounting for 81% of total costs among children 0–14 years old. Laboratory commodities were the second largest contributor to total cost, followed by human resources and co-trimoxazole *(141)*.

Implementation considerations

As ART is expanded to all children regardless of clinical and immune status, children younger than two years or children with WHO stage 3 or 4 disease or CD4 percentage below 25% or CD4 count at or below 750 cells/mm^3 (if younger than five years) and CD4 counts at or below 350 cells/mm^3 (if older than five years) should be given priority for treatment because of their higher risk of death and rapid disease progression.

Implementation approaches should include using opportunities to deliver ART for children in maternal, newborn and child health settings *(175)*.

Expanding ART services for children will require strategies to improve retention in care and to support adherence. Careful clinical monitoring remains essential to assess the risk of treatment failure, but lack of laboratory monitoring should not be a barrier to initiating ART *(176)*.

Research gaps

How earlier ART affects retention, adherence and potential HIV drug resistance among children with less advanced disease needs to be investigated further. Optimal service delivery models to ensure rapid identification and ART initiation among infants and children also need to be investigated. Strategies are needed to provide an integrated package of care to reduce overall child mortality.

2.2 Oral pre-exposure prophylaxis for preventing the acquisition of HIV infection

Recommendation

NEW

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

Background

Oral PrEP is the use of ARV drugs by HIV-uninfected people to block the acquisition of HIV before exposure to HIV.

Twelve trials of the effectiveness of oral PrEP have been conducted among serodiscordant couples, heterosexual men, women, men who have sex with men, people who inject drugs and transgender women *(177–188)*. Where adherence has been high, significant levels of efficacy have been achieved, showing the value of this intervention as part of combination prevention approaches.

In 2012, WHO recommended PrEP for use among serodiscordant couples, men who have sex with men and transgender people on the basis that demonstration projects were needed to ascertain optimal delivery approaches *(189)*. In 2014, WHO developed consolidated HIV guidelines for key populations, including men who have sex with men, people who inject drugs, sex workers, transgender people and people in prisons and other closed settings *(190)*. In those guidelines, PrEP was strongly recommended for men who have sex with men.

This new recommendation replaces the previous WHO recommendations on PrEP and enables the offer of PrEP to be considered for people at substantial risk of acquiring HIV rather than limiting the recommendation to specific populations. Box 3 discusses the definition of "substantial risk". The new recommendation will enable a wider range of populations to benefit from this additional prevention option. It also allows the offer of PrEP to be based on individual assessment, rather than risk group, and is intended to foster implementation that is informed by local epidemiological evidence regarding risk factors for acquiring HIV.

Box 3. 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 some groups of men who have sex with men, transgender women in many settings 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 this recommendation identified and recruited groups at substantial risk of acquiring HIV infection, as demonstrated by the HIV incidence rate among participants in control arms that ranged between 3 to 9 per 100 person-years in most studies. Indeed, the HIV incidence in control arms of PrEP trials was often higher than anticipated, suggesting that PrEP attracts people at particularly high risk *(187)*. In locations where the overall incidence of HIV infection is low, there may be individuals at substantial risk who would be attracted to PrEP services.

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 *(191)*. Thresholds for offering PrEP may vary depending on a variety of considerations, including available resources and the relative costs, feasibility and demand for PrEP and other opportunities.

Rationale and supporting evidence

A systematic review and meta-analysis of PrEP trials containing TDF demonstrated that PrEP is effective in reducing the risk of acquiring HIV infection *(192)*. The level of protection did not differ by age, gender, regimen (TDF versus FTC + TDF) and mode of acquiring HIV (rectal, penile or vaginal). The level of protection was strongly correlated with adherence.

HIV infection

HIV infection was measured in 11 randomized controlled trials comparing PrEP to placebo, three randomized controlled trials comparing PrEP to no PrEP (such as delayed PrEP or "no pill") and three observational studies. Across data from 10 trials comparing PrEP with placebo, the results from a meta-analysis demonstrated a 51% reduction in risk of HIV infection for PrEP versus placebo *(192)*.

Mode of acquisition

When studies were stratified by mode of acquisition (rectal, vaginal or penile exposure), PrEP showed similar effectiveness across groups. The relative risk of HIV infection for PrEP versus placebo for rectal exposure is 0.34 (95% CI: 0.15–0.80, $P = 0.01$). For penile or vaginal exposure, the relative risk of HIV infection for PrEP versus placebo is 0.54 (95% CI: 0.32–0.90, $P = 0.02$) *(192)*. Parenteral exposure to HIV was not analysed separately because only one study explicitly included people who inject drugs, and their exposure to HIV arose from sexual practices and incomplete access to sterile injection equipment.

Sex and gender

Of the 10 randomized PrEP trials reporting HIV outcomes, women were included in six studies and men in seven studies. PrEP was effective for both men and women. The relative risk of HIV infection for PrEP versus placebo was 0.57 (95% CI 0.34–0.94; $P = 0.03$) among women and 0.38 (95% 0.20–0.60; $P = 0.0001$) among men. Two placebo-controlled trials that targeted women exclusively showed very low uptake of PrEP (less than one third) in the active arm and no effectiveness on an intent-to-treat basis *(183,186)*. PrEP effectiveness among women in four trials that included both women and men was higher. For example, among women younger than 30 years in a trial that included both men and women, the effectiveness was 72% (95% CI: 29–92%, $P = 0.01$) for TDF and 77% (95% CI: 25–90%, $P = 0.01$) for FTC + TDF PrEP *(180)*. The results from a recent study (HPTN 067) among young, predominately single South African women receiving open-label FTC + TDF as PrEP showed that young women can maintain adherence, with 80% having substantial concentrations of drug detected at week 4 and 65% at week 24 in the daily PrEP arm *(193)*. More information about PrEP in transgender populations is needed.

Adherence

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

When studies were stratified according to adherence levels (high, moderate and low), heterogeneity was greatly reduced within adherence subgroups, demonstrating that most heterogeneity between studies can be explained by differing adherence levels. Within adherence subgroups, PrEP is the most efficacious among the high-adherence group (defined as >70% drug

detection, but all studies in this group had adherence at or above 80%) and significantly reduces the risk of acquiring HIV infection in studies with moderate levels of adherence (41–70% drug detection). Among studies with low adherence (40% or lower drug detection), PrEP shows no effect in reducing HIV infection *(192)*.

Safety

Ten randomized controlled trials comparing PrEP with placebo presented data on any adverse event. The risk of experiencing at least one adverse event during follow-up was common in participants in all trials. Across studies, the rates of any adverse event did not differ for PrEP versus placebo. Similarly, there were no differences across subgroups, including mode of acquisition, adherence, sex, drug regimen, drug dosing or age.

Eleven randomized controlled trials comparing PrEP with placebo presented the results for any grade 3 or 4 adverse event. Across studies, there was no statistical difference in rates of any grade 3 or 4 adverse event for PrEP versus placebo and there were no statistical differences across subgroup analyses, including adherence, sex, drug regimen, drug dosing or age *(192)*.

Several studies noted subclinical declines in renal functioning and bone mineral density among PrEP users *(194–196)*. These subclinical changes did not result in clinical events and were not progressive over time.

Drug resistance

The risk of drug resistance to FTC was overall low (11 people with FTC- or TDF-resistant HIV infection among 9222 PrEP users, or 0.1%), and this occurred mainly among people who were acutely infected with HIV when initiating PrEP: 7 people with FTC- or TDF-resistant HIV infection among 9222 PrEP users. The proportion of people with drug-resistant HIV infection did not differ in the PrEP and placebo groups among everyone at risk, although the number of events was low (n = 6 people infected). Multiple HIV infections (8–50) were averted for every case of FTC resistance associated with starting PrEP in the presence of acute HIV infection *(192)*. Modelling the HIV drug resistance resulting from ART is predicted to far exceed that resulting from PrEP *(197)*. Although mathematical models inform the risk of resistance, their results rely on data from clinical trials and make assumptions about risk of drug resistance selection during PrEP. How implementing PrEP on a large scale affects resistance overall is unknown, and active surveillance during PrEP scale-up may therefore be warranted.

Sexual and reproductive health outcomes

No evidence indicated that PrEP led to risk compensation in sexual practices, such as decreased condom use or more sexual partners *(198,199)*.

PrEP does not appear to affect the effectiveness of hormonal contraception, although two studies found trends towards higher rates of pregnancy among oral contraceptive users who also took PrEP. When multivariate analysis accounted for confounders, this relationship became nonsignificant. Oral PrEP was not associated with increased adverse pregnancy-related events among women taking PrEP during early pregnancy *(180,186)*. More information is needed about interactions between PrEP and the hormone therapy used by transgender populations.

The review sought to evaluate the effectiveness of PrEP in preventing HIV infection in the context of access to a combination of standard approaches to HIV prevention *(192)*. Across all trials, PrEP was provided in the context of a package of HIV prevention interventions, including regular HIV testing and counselling, provision of condoms, screening and treatment for sexually transmitted infections, adherence counselling and other options relevant to the study population, such as access to contraception for women and methadone maintenance for people who inject opioids.

Cost and cost–effectiveness

The HIV incidence threshold for cost-saving implementation of PrEP will vary depending on the relative costs of PrEP versus treatment for HIV infection and the anticipated effectiveness of PrEP. In some situations, PrEP may be cost saving, but other interventions may be more cost saving and scalable. Monetary costs should not be the only consideration, since staying free of HIV and having control over HIV risk is of intangible value to people and communities.

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

A review of cost–effectiveness studies for PrEP found that, in generalized epidemics, giving priority for the use of PrEP to people at substantial risk of acquiring HIV infection increases impact *(200)*. Some of these studies found PrEP to be cost-effective within the context of ART expansion; others found no benefit. Among concentrated epidemics (such as men who have sex with men in the United States), PrEP could significantly impact the epidemic. Studies have found PrEP to be cost-effective depending on the cost of the drug and delivery systems when PrEP uptake is higher among people at substantial risk. Higher PrEP uptake and adherence have been observed among men who have sex with men in demonstration projects *(178,193)*. The results vary widely depending on epidemic type, location and model parameters, including efficacy, cost, HIV incidence and target population *(201)*.

Equity and acceptability

Preventing HIV infection among PrEP users will contribute to equitable health outcomes by sustaining their health and the health of their sexual partners. Access to PrEP also provides opportunities for accessing sexual health services, and people at substantial HIV risk are often currently medically underserved and have few other effective HIV prevention options. Extending PrEP recommendations beyond narrowly defined groups (such as men who have sex with men and serodiscordant couples) allows for more equitable access and will reduce future treatment costs overall by preventing HIV infection in populations with a high incidence.

PrEP acceptability has been reported in multiple populations: women, serodiscordant couples, female sex workers, young women, people who inject drugs, transgender people, service providers and men who have sex with men. A qualitative literature review (Annex 2) (131 peer-reviewed articles and 46 abstracts) showed that individuals have substantial interest in accessing PrEP as an additional choice for HIV prevention. Population support for provision of PrEP was based on the knowledge of safety and effectiveness and the compatibility of PrEP with other prevention strategies.

Feasibility

Oral PrEP for diverse populations has proven feasible in multiple trial settings and demonstration projects. Two placebo-controlled trials among women *(183,186)* found significant barriers to uptake and adherence. However, programme settings differ from trials. PrEP adherence among women has been high when open-label PrEP is provided (HPTN 067 ADAPT Study and the TDF2 Open Label Extension) *(202,203)*.

The iPrEx OLE project and the Partners Demonstration project both show that PrEP implementation is feasible for different populations, including men and women *(177,178)*. The PROUD study, conducted in the United Kingdom and designed to mimic real-life settings,

demonstrated that PrEP is feasible and effective and is not associated with significant changes in behavioural risk (*187)*. Other PrEP demonstration projects in Botswana, South Africa, Thailand and the United States of America confirm that protective levels of adherence are feasible for most PrEP users *(202–207)*, although challenges remain to achieve high levels of adherence among young people *(207)*.

Implementation considerations

There are significant concerns about implementing PrEP, especially in legal environments in which the rights of people at substantial risk of HIV are violated. PrEP should not displace or threaten the implementation of effective and well established HIV prevention interventions, such as condom programming and harm reduction. Stigma is a driver of HIV and could be decreased or increased depending on the how PrEP is implemented. PrEP should be promoted as a positive choice among people for whom it is suitable and their communities, in conjunction with other appropriate prevention interventions.

WHO will publish comprehensive implementation guidance for PrEP in 2016. The implementation guidance will include practical suggestions for human resource utilization, laboratory monitoring, pharmacy services, drug procurement, counselling, communication, community engagement, coordination of services (including testing, treatment, PrEP, post-exposure prophylaxis and other sexual and reproductive health services) and programme management. The implementation guidance is briefly summarized here. Health-care providers should be trained and supported so that they can explore sexual and injecting risk behaviour with people and help them consider their risk of acquiring HIV infection and the range of prevention options, including PrEP. This requires providing respectful and inclusive services, a familiarity with techniques for discussing sensitive behaviour and a strong patient–provider relationship that enables discussions of facilitators and barriers to engagement in health-care services, adherence and self-care. Service providers should be aware of the emotional and physical trauma that people at substantial risk of acquiring HIV infection may have experienced *(208)*. The capacity for respectful work with people who have experienced trauma involves communication and skills development. Developing services that are suited to young people, especially young women and key populations, is essential for the success of all HIV treatment and prevention programmes, including PrEP.

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

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

People at substantial risk of acquiring HIV are often medically underserved, have few other effective HIV prevention options and may face social and legal challenges. Providing PrEP may

give opportunities for increased access to a range of other health services and social support, including vaccinations for hepatitis B, reproductive health services, sexual health services (including managing sexually transmitted infections), mental health services and primary health care.

HIV testing is required before PrEP is offered and regularly while PrEP is taken. Using quality-assured HIV testing is important, and using more sensitive tests has multiple advantages, including earlier HIV diagnosis and treatment, better counselling for people with acute HIV infection and minimizing the risk of drug resistance during pre- and post-exposure prophylaxis. Rapid point-of-care third-generation HIV antibody tests that use whole blood obtained by finger-stick or phlebotomy are available and are preferred to the use of oral fluids or second-generation tests when starting PrEP. Referral of people who test positive to HIV treatment services is essential.

All PrEP trials tested renal function using serum creatinine before starting PrEP and at least quarterly during PrEP use, and these test results were used to exclude participants from trials and to stop study medication for abnormal results that were confirmed by repeat testing. Renal function returned to normal after stopping PrEP except for a few people who had underlying comorbidities such as systemic hypertension and diabetes mellitus. Unless more data become available, creatinine testing is preferred before starting PrEP and quarterly during PrEP use for the first 12 months then annually thereafter. Point-of-care and laboratory-based assays for creatinine and HIV are available.

Hepatitis B is endemic in many parts of the world where HIV is transmitted. The medications used for PrEP are active against hepatitis B. Withdrawal of active therapy against HBV infection can lead to virological and clinical relapse. Clinical relapse did not occur during or after PrEP use in trials that included people with chronic hepatitis B *(182,184)*. These trials excluded people with clinical liver cirrhosis and people with significant elevations in liver function tests. Testing PrEP users for hepatitis B surface antigen (HBsAg) is preferred. People with detectable HBsAg and ALT elevated more than twice the upper limit of normal or clinical signs of cirrhosis could benefit from long-term therapy for hepatitis B infection. Rapid point-of-care tests are available for HBsAg.

PrEP should always be provided together with other HIV prevention options. Community-based organizations working with key populations could play a significant role in reaching people at higher risk, informing them about PrEP availability as well as about when PrEP should be used, providing informational support and linkage to health-care services for those who are interested. Links to community-based organizations and peer support will be particularly helpful for people from key populations and young people, especially young women. Community-based organizations should play a significant role in engaging people at substantial risk, providing information about PrEP availability, identifying when PrEP should be considered, how PrEP should be integrated with essential services required for sexual and reproductive health. Harm-reduction interventions, including access to sterile or new injection materials, are the mainstay of preventing HIV infection from injections, and such supplies should be made available to anyone using injected substances or medications. Condoms and lubricants must be made available, including for sex workers, who should be empowered to insist on their use.

PrEP is only effective when used. The most important way to support adherence is to offer PrEP as a choice. Support for adherence should include information that PrEP is highly effective when used and that consistent use requires that the medications be included in people's daily routine. Support groups for PrEP users, including groups formed on social media (for example, https://www.facebook.com/groups/PrEPFacts) are helpful for peer-to-peer sharing of experience and solutions. Brief client-centred counselling that links daily medication use with a daily habit (such as waking up, going to sleep or a regular meal) is helpful. Special programmes to facilitate adherence among young people and women may be needed. People who start PrEP may report

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

PrEP can be discontinued if a person taking PrEP is no longer at risk and when this is likely to be sustained. Engaging with community support groups is important to facilitate the recognition of circumstances that involve substantial risk of acquiring HIV. PrEP is needed during periods of risk rather than for life. Such periods of risk may begin and end with changes in relationship status, alcohol and drug use, leaving school, leaving home, trauma, migration or other events. PrEP users should be advised that five to seven days of PrEP are needed before achieving full protection for anal intercourse. Preliminary pharmacological studies suggest that nearly 20 days of PrEP are needed before achieving full protection for vaginal intercourse *(209)*. People who report exposure to HIV before full protection from PrEP has been achieved should be considered for post-exposure prophylaxis (PEP) *(210)*. As with PEP, PrEP may be discontinued 28 days after the last potential exposure to HIV-infected fluids if people do not have continuing substantial risk for acquiring HIV infection.

Pregnancy is associated with a higher risk of acquiring HIV infection, and HIV infection acquired during pregnancy or breastfeeding is associated with an increased risk of HIV transmission to the infant. In PrEP trials, exposure to TDF-containing PrEP during the first trimester of pregnancy was not associated with adverse pregnancy or infant outcomes. Evidence is growing of the safety of TDF and FTC + TDF during pregnancy and breastfeeding when used for treating maternal HIV or hepatitis B *(211)*. Contraception services, safer conception management and links to antenatal care should be available when providing PrEP services for women. The risks, benefits and alternatives of continuing to use PrEP during pregnancy and breastfeeding should be discussed with each person. Further research is needed to fully evaluate PrEP use during pregnancy and breastfeeding.

New WHO recommendations for treatment and PrEP are expected to facilitate the identification of people recently infected with HIV. Whenever possible, people in their social and sexual networks should be offered HIV testing, treatment, and prevention services. PEP and PrEP should be considered, in combination with other prevention services, for HIV uninfected partners of recently diagnosed people.

Research gaps

Operational research is needed in diverse settings to generate demand for prevention services (including PEP and PrEP) and to identify and engage people at substantial risk for HIV. Additional research is needed on how to support adherence, especially for adolescents, young women and transgender men and women. Such research should generate practical knowledge and skills through implementation.

Severe long-term toxicity of TDF for HIV treatment is rare. Surveillance of large-scale use of PrEP could identify rare but important clinical adverse events. For outcomes with few events (drug resistance and reproductive health outcomes), active surveillance during PrEP scale-up is warranted. WHO provides a range of guidance on toxicity monitoring *(212)*.

The impact of PrEP on sexual practices may vary according to social and cultural contexts. The implementation of PrEP in diverse situations will provide opportunities for understanding how PrEP influences sexual practices, which may include improved sexual health and emotional well-being, a decrease of stigma and discrimination towards people living with HIV or increased use of other HIV prevention methods. Adverse behavioural and social outcomes are also possible, although they have not been observed so far. The role of gender norms may also influence

the uptake of prevention and treatment services, including PrEP, and could be useful focus for qualitative implementation research.

The Ipergay trial showed high-level efficacy of PrEP dosing before and after sex among men who have sex with men who reported frequent sexual activity *(204)*. The HPTN 067 trial randomly compared recommendations for daily and non-daily PrEP regimens and found that the daily recommendation was associated with the highest concentrations of drug, the highest adherence and high coverage of sex events with pre- and post-exposure dosing among men who have sex with men in Bangkok and New York and women in Cape Town *(202,204,205)*. Medication requirements and use were also higher for those randomized to a recommendation for daily use. Daily dosing was the preferred recommendation, or a preferred recommendation, for the majority of users. How best to adapt PrEP recommendations to diverse and changing sexual practices is an important focus for implementation research.

PrEP costs are substantial, and include costs for clinic staff, medications, laboratory testing, pharmacy services, community education, provider education and monitoring and evaluation. Implementation research should include evaluation of strategies for minimizing costs that do not compromise safety, effectiveness or the quality of information provided to prospective PrEP users. Ways to negotiate lower prices for medications and laboratory tests could be developed using volume purchasing. PrEP is amendable to algorithmic care, which would enable task sharing with less costly and more available staff. Research is needed to determine whether HIV status and renal function can be less frequently monitored without increasing the risk of adverse clinical outcomes. Optimal recommendations for starting and stopping PrEP to maximize use during periods of substantial risk would decrease medication requirements and increase the impact on HIV transmission.

Additional research on how best to integrate PrEP services with other services is needed. PrEP is compatible with HIV testing, HIV treatment services, sexual health services, condom provision, behavioural counselling, harm reduction, empowerment programmes, contraceptive services, reproductive health services and primary health care. PEP started after recent exposure to HIV can be transitioned to PrEP after 28 days if there is continuing substantial risk. How best to integrate PrEP into these existing services is not known and may vary in different locations.

2.3 Programmatic note on the recommendations

Guidance on service delivery

A wide range of operational considerations needs to be addressed as countries begin dialogue and planning to implement the recommendations in this guideline. The complete update to the consolidated WHO ARV guidelines to be published in 2016 will include programmatic and operational guidance based on evidence reviews for key PICO questions on operational issues, including the following topics related to the care of individuals living with HIV:

- frequency of clinic visits and medication pick-ups for stable patients;
- interventions to facilitate linkage to care, retention in care and adherence to medication; and
- strengthening services, including task shifting and integration of care.

Implementation guidance for PrEP will also be published in 2016. In addition, the recently published consolidated guidelines on HIV testing services *(213)* and strategic information *(214)* will be of value to countries to identify people living with HIV and to ensure that countries effectively monitor their programmes.

CD4 count and viral load monitoring

During the past decade, WHO guidelines for ART in low- and middle-income countries have evolved towards recommending that countries phase in viral load for monitoring treatment and, since 2013, WHO has recommended viral load monitoring as the preferred approach to monitor patient response to ART. Most countries have adopted this recommendation and are in the process of scaling up viral load monitoring capacity.

Previously, the main way to monitor response to ART was through either clinical or immunological (CD4 cell count) monitoring, and in settings where both immunological and virological monitoring is available, both are generally done.

Given the recommendations in this guideline to initiate ART at any CD4 count, it may be reasonable to reduce or stop CD4 cell count for monitoring in settings where viral load monitoring can be assured. Nevertheless, CD4 count testing still has an important role to play in assessing baseline risk of disease progression, for starting and stopping prophylaxis and in making priority-setting decisions regarding ART initiation in settings where universal treatment is not possible. CD4 cell count measurement may also be important for individuals for whom ART is failing.

The complete update of the consolidated ARV guidelines will include updated recommendations and operational guidance on clinical monitoring, including use of CD4 count and viral load testing.

Adherence

Adherence to ART is a primary determinant of viral suppression and risk of transmission, disease progression and death. Suboptimal adherence is a major challenge in all regions, at all stages of HIV disease, and is associated with a diversity of patient- and programme-related challenges. Individual factors may include forgetting doses; being away from home; changes in daily routines; depression or other illness; limited understanding of treatment benefits; a lack of interest or desire to take the medicines; and substance or alcohol use. Adherence to ART may also be challenging in the absence of supportive environments for people living with HIV and because

of HIV-related stigma and discrimination. Medication-related factors may include adverse events; the complexity of dosing regimens; the pill burden; and dietary restrictions. Health system factors include distance to health services; long waiting times to receive care and obtain refills; and the burden of the direct and indirect costs of care.

Specific population groups facing additional adherence challenges may include pregnant and postpartum women, adolescents, infants and children, key populations and people with mental health and substance use disorders.

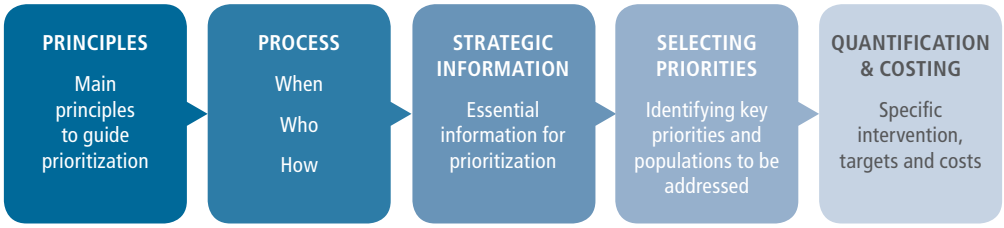
Long-term adherence to treatment is critical for the success of ART and presents new challenges as PrEP programmes are brought to scale. The updated consolidated ARV guidelines to be published in 2016 will provide guidance on adherence support based on updated evidence and lessons from recent programmatic experience.

Setting priorities

The impact of these guidelines will be determined by the extent to which they are implemented in the specific country contexts. Although global and national HIV goals are becoming more ambitious and aim to ultimately end AIDS by 2030, many low- and middle-income countries may have limited available resources and implementation capacity. It is therefore important that informed choices be made on implementing these guidelines.

WHO has developed a draft priority-setting framework for HIV and other similar communicable disease programmes (Fig. 4). The purpose of the framework is to provide a structured approach by which national stakeholders can address issues of priority-setting in the face of competing programme needs and limited available resources. The framework outlines issues to be considered in setting priorities but does not make specific recommendations on what should be given priority, as these decisions are highly context and country specific. The details of this framework will be made available in the complete update to the consolidated ARV guidelines to be published in 2016.

Fig. 4. WHO generic framework for setting priorities



PUBLICATION, DISSEMINATION AND EVALUATION

03

3. PUBLICATION, DISSEMINATION AND EVALUATION

This guideline will be incorporated into the full update of the 2013 consolidated guidelines for the use of ARV drugs for treating and preventing HIV infection. Review and update of the full guideline will be planned for every 2–3 years. As the evidence base or user's needs change, consideration will be given to technically updating the relevant section.

This guideline will be launched as a web-based product for initial dissemination. Dissemination will be supported by peer-reviewed publication of the systematic reviews and evidence. The WHO Department of HIV/AIDS will work closely with WHO regional and country offices to ensure further communication and country adaptation of these two recommendations.

An evaluation process will be conducted building on the 2014 and 2015 evaluation surveys to identify the uptake of the guideline into policy.

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Annex 1. Declaration of interests, Clinical Guideline Development Group, June 2015

Key

Declaration of conflict of interest

- None – no conflict declared on conflict of interest form or at start of the Clinical Guideline Development Group meeting in June 2015
- 0 – no conflict declared
- 1 – conflict declared with public disclosure statement

Management plans

- Conditional participation: continued involvement in the meeting and publicly disclose the expert's interest at the start of the meeting and in the report of the meeting and relevant publications or work products.
- Partial exclusion: limited involvement: (a) exclude expert from that portion of the meeting or work where conflict of interest has been identified and/or exclude the expert from participating in the decision-making process. Reported interest to be publicly disclosed to other meeting participants and in the report of the meeting and relevant publications or work products. Partial exclusion was carefully monitored in the meeting.
- Total exclusion: expert was excluded from the meeting altogether.

PICO questions

A1.1 In adults, adolescents and children with HIV, is ART initiated at a threshold above CD4 500 cells/mm^3 compared with less than 500 cells/mm^3 more harmful?

A1.3 Should pregnant and breastfeeding women with HIV started on triple ARV drugs continue on lifelong ART regardless of eligibility criteria?

E1.1 Should oral PrEP containing TDF be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches?

	Financial significant	Non-financial significant
PICOs A1.1, A1.3 and E1.1	2	3
Other PICOs in 2015 guideline early release	11	1

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan	
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
			Employment	Consulting	Research support	Non-monetary support	Stocks, bonds, stock options and securities	Commercial business interests	Patents, trademarks or copyrights	Proprietary know-how in a substance, technology or process	Expert opinion or testimony for commercial entity or organization	Office or position to represent interest relating to subject of the meeting or work			PICO A1.1, A1.3 and E1.1 (relevant to this guideline)	Other PICOs (Relevant to full update)
Elaine Abrams ICAP, Columbia University (Co-Chair)	AMR	USA	0	1 Participation in advisory board GKS/ViiV Healthcare USD 4500	0	1 Principal investigator for implementation science study; Merck donated ARV drugs	0	0	0	0	0	0	0	0	Financial non-significant Non-financial significant	
															Partial exclusion from the decision-making process or voting for relevant PICOs A1.1 and A1.3	
Serge Eholie University Felix Houphouet-Boigny (Co-Chair)	AFR	Côte d'Ivoire	0	0	0	0	0	0	0	0	0	0	Principal investigator for TEMPRANO study	0	Non-financial significant	
															Partial exclusion from the decision-making process or voting for relevant PICOs; did not chair discussion on when to start A1.1 and A1.3	
Renaud Becquet INSERM-Bordeaux University	EUR	France	0	0	0	0	0	0	0	0	0	0	0	0	None	
Alexandra Calmy Geneva University Hospital	EUR	Switzerland	0	0	1 Travel grant, research grants (unrestricted), support for the metabolic clinic. AbbVie, Janssen, Cilag, Gilead, Boehringer, ingelheim. MSD, BMS, ViiV Healthcare, CHF 10 000 each		0	0	0	0	0	0	0	0	Financial significant	
																Partial exclusion from the decision-making process or voting for relevant PICOs

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Pedro Cahn Fundacion Huesped	AMR	Argentina	0	1	1 Research grants Abbvie, Merck, ViiV Healthcare Served on advisory boards for Merck, ViiV Healthcare and Abbvie		0	0	0	0	0	0	0	0	Financial significant Partial exclusion from the decision-making process or voting for relevant PICOs
Sergio Carmona NHLS	AFR	South Africa	0	0	1 Research grants to research unit (multiple) Technical advisory board, CROI 2014, Abbott, USD 1000 Speaker, IAS 2014, Abbott, travel cost only		0	0	0	0	0	0	0	0	Financial significant Conditional participation through disclosure of his interests Institutional research support only
Mohammed Chakroun Teaching Hospital and University of Monastir	EMR	Tunisia	0	0	0	0	0	0	0	0	0	0	0	0	None
Nikoloz Chkhartsihvili Infectious Diseases, AIDS and Clinical Immunology Research Center	EUR	Georgia	0	0	0	0	0	0	0	0	0	0	0	0	None
Martin Choo Asia Pacific Network of People Living with HIV	SEAR	Malaysia	0	1 Consulting community consultations to support WHO 2015 ARV guidelines, USD 6000	0	0	0	0	0	0	0	1 Unpaid invited presentation at 2015 Social Forum by the United Nations Human Rights Council	1 Person living with HIV who depends on HIV treatment for survival and well-being.	0	Financial non-significant Non-financial non-significant
David Cooper Kirby Institute	WPR	Australia	0	0	1 Research support BMGF, Gilead, ViiV Healthcare	0	0	0	0	0	0	0	1 Site investigator for ENCORE and site investigator for START	0	Financial significant Non-financial significant

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan	
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
					Merck to employer										Partial exclusion from the decision-making process or voting for relevant PICOs A1.1 and A1.3	
Mark Cotton Stellenbosch University	AFR	South Africa	0	0	1 NIH research grant–employer	0	0	0	0	0	0	0	0	0	Financial significant Conditional participation through disclosure of his interests Institutional research support only	
Aleny Couto Ministry of Health, Mozambique	AFR	Mozambique	0	0	0	0	0	0	0	0	0	0	0	0	None	
Wondwossen Amogne Degu Addis Adaba University School of Medicine	AFR	Ethiopia	0	0	0	0	0	0	0	0	0	0	0	0	None	
Charles Flexner Johns Hopkins University	AMR	USA	0	1 Current consulting fees: Merck, USD 19 000 Mylan Pharmaceuticals, USD 13 000 Per diem for consulting services related to drug development or clinical pharmacology	1 Unrestricted grant to Johns Hopkins University (employer) for investigator support	0	0	0	0	0	0	0	0	0	Financial significant Partial exclusion from the decision-making process or voting for relevant PICOs	

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan	
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
Peter Fonjungo United States Centers for Disease Control and Prevention	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None	
Carlo Giaquinto University of Padova	EUR	Italy	0	1 Advisory board, ViiV Healthcare, €2500 Gilead, €2500	1 Research support to research unit 2014–current: Gilead, BMs, Jenssen, ViiV Healthcare	0	0	0	0	0	0	0	0	0	Financial significant	Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only
Diane Havlir University of California San Francisco	AMR	USA	0	0	1 Research support from NIH to support UCSF faculty salary Research support	0	0	0	0	0	0	0	0	0	0	Financial non-significant
Charles Holmes Centre for Infectious Disease Research in Zambia and Johns Hopkins University	AMR	USA	0	1 Consulting on content and strategy for continuing medical education, USD 10 000	1 Research support pending from BGMF to employer, USD 40 000	0	0	0	0	0	0	0	0	0	0	Financial non-significant
John Idoko National Agency for the Control of AIDS	AFR	Nigeria	0	0	0	0	0	0	0	0	0	0	0	0	0	None

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan	
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
Andreas Jahn ITECH	AFR	Malawi	0	0	0	0	0	0	0	0	0	0	0	0	None	
Quarraisha Abdool Karim CAPRISA	AFR	South Africa	0	0	0	1 Honorarium of USD 2000 from Gilead	0	0	1 Patent for use of tenofovir to prevent HSV-2 infection	0	0	0	1 Principal investigator for CAPRISA 004 and CAPRISA 008 and principal investigator for HPTN 077	0	Financial non-significant Non-financial significant	Partial exclusion from the decision-making process or voting for relevant PICOs
Nagalineswaran Kumarasamy YRGCARE Medical Centre, VHS, Chennai India	SEAR	India	0	0	0	0	0	0	0	0	0	0	0	0	None	
Karine Lacombe Sorbonne-University and INSERM AP-HP	EUR	France	0	1 Board adviser, BMS, Gilead, MSD, Abbvie, Janssen, USD 10 000	1 Board adviser, BMS, Gilead, MSD, Abbvie, Janssen, USD 10 000	1 Board advisor, BMS, Gilead, MSD, Abbvie, Janssen, USD 10 000	0	0	0	0	0	0	0	0	Financial significant	Partial exclusion from the decision-making process or voting for relevant PICOs
Loyce Maturu AFRICAID ZANDIRI	AFR	Zimbabwe	0	0	0	0	0	0	0	0	0	0	0	0	None	
Dorothy Mbori-Ngacha UNICEF	AFR	South Africa	0	0	0	0	0	0	0	0	0	0	0	0	None	
Landon Meyer University of Cape Town	AFR	South Africa	0	0	0	1 Alere Health Care, USD 20 000 in	0	0	0	0	0	0	0	0	Financial significant	

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan	
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
						Equipment										Partial exclusion from the decision-making process or voting for relevant PICOs Institutional research support only
Lynne Mofenson Elizabeth Glaser Pediatric AIDS Foundation	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None	
Angela Mushavi Ministry of Health and Child Care, Zimbabwe	AFR	Zimbabwe		0	0	0	0	0	0	0	1 Coordinate PMTCT and HIV care and treatment for children in Zimbabwe and interested technically in the outcome of the meeting	0	1 The outcome of the meeting leads to revised WHO recommendations for PMTCT and HIV care and treatment for children and will affect the programme in Zimbabwe	0	Financial non-significant Non-financial non-significant	
Angelina Namiba Positively UK	EUR	UK	0	0	0	0	0	0	0	0	0	0	0	0	None	
Shinichi Oka National Centre for Global Health and Medicine	WPR	Japan	0	0	0	0	0	0	0	0	1 Travel to meeting supports by employer	0	0	0	Financial non-significant	
Ryan Phelps United States Agency for International Development	AMR	USA	0	0	0	0	0	0	0	0	1 Travel to meeting supports by employer	0	0	0	Financial non-significant	
Andrew Prendergast MRC University of London	EUR	UK	0	0	0	0	0	0	0	0	0	0	0	0	None	

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products	
Elliot Razies United States Centers for Disease Control and Prevention	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None
George Siberry United States National Institutes of Health	AMR	USA	0	0	0	0	0	0	0	0	0	0	1 Contribution towards travel costs	0	Financial non-significant
Annette Sohn TREAT ASIA – amfAR	SEAR	Thailand	0	0	1 Research and training grants to institution Medicine donation for research study on hepatitis C to research unit only	0	0	0	0	0	0	0	0	0	Financial significant Conditional participation through disclosure of interests Institutional research support only
Bukiki Sylvere Biziyaremye ITPC West Africa	AFR	Côte d'Ivoire	0	0	0	0	0	0	0	0	0	0	0	0	None
Denis Tindyebwa ANECCA	AFR	Uganda	0	0	0	0	0	0	0	0	0	0	0	0	None
Francois Venter Wits RHI	AMR	South Africa	0	1 Travel support to IAS, Gilead and Mylan, USD 2000	1 Principal investigator for BMGF low-dose stavudine; principal investigator for low-dose darunavir ; SA MRC investigator for PrEP and TandT in sex workers; Gilead and Mylan, donation of drug	1	0	0	1 Advisory boards, Jansen, Tibotech and Mylan, USD 500 to USD 1000 per meeting	1 Speaking honoraria, Merck, GSK, USD 500 per meeting	0	0	0	0	Financial significant and Non-financial significant interest
Heather Watts Office of the Global AIDS Coordinator, United States Department of State	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None

Name, institution	WHO region	Country	Declaration of conflict of interest												Conflicts and management plan	
			Employment and consulting		Research support		Investment interests		Intellectual property		Public statements and positions		Additional information	Tobacco products		
Heather Watts Office of the Global AIDS Coordinator, United States Department of State	AMR	USA	0	0	0	0	0	0	0	0	0	0	0	0	None	
Benjamin Young International Association of Providers of AIDS Care	AMR	USA	0	0	1 Research support, Merck and Co., Gilead Sciences and ViiV Healthcare	1 Advisory boards, Bristol Myers Squibb, Merck and Co. and ViiV Healthcare	0	0	0	0	0	0	0	0	Financial significant interest	Partial exclusion from the decision-making process or voting for relevant PICOs
Oleg Yurin Central Research Institute of Epidemiology	EUR	Russian Federation	0	0	0	0	0	0	0	0	0	0	0	0	None	
Fuji Zhang NCAIDS Chinese CDC	WPR	China	0	0	0	0	0	0	0	0	0	0	0	0	None	
Methodologist																
Nandi Siegfried Independent clinical epidemiologist	AFR	South Africa	0	1 Consulting as methodologist for WHO, 2011–2015, remuneration > USD 40 000	0	0	0	0	0	0	0	0	0	0	Financial non-significant	

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