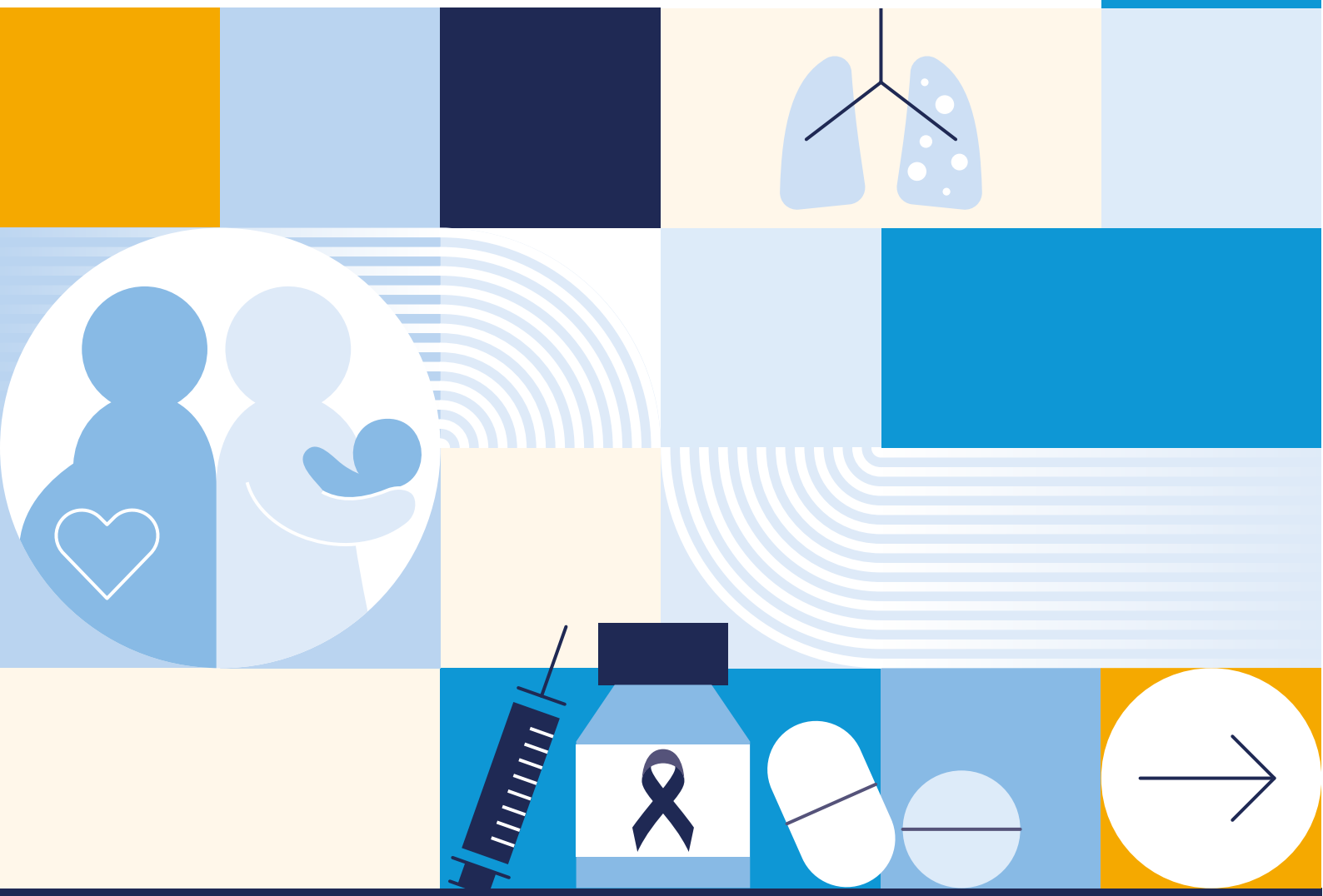
WHO updated recommendations on HIV clinical management: recommendations for a public health approach



World Health Organization

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Contents

Web Annex. Supporting information

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Acronyms and abbreviations

1HP	1 month of daily isoniazid + rifapentine
2DR	two-drug antiretroviral regimen
3DR	three-drug antiretroviral regimen
3HP	3 months of weekly isoniazid + rifapentine
3HR	3 months of daily isoniazid +rifampicin
3TC	lamivudine
4R	4 months of daily rifampicin
6H/9H	6 or 9 months of daily isoniazid
6Lfx	6 months of daily levofloxacin
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral
ATV/r	atazanavir/ritonavir
AZT	zidovudine
CAB	cabotegravir
DALYs	disability-adjusted life years
DRV/r	darunavir/ritonavir
DTG	dolutegravir
EFV	efavirenz
eGFR	estimated glomerular filtration rate
EID	early infant diagnosis
FDC	fixed-dose combination
FTC	emtricitabine
HIV	Human Immunodeficiency Virus
HIVTSQ	HIV Treatment Satisfaction Questionnaire Score
INH	isoniazid
INSTI	integrase strand transfer inhibitor
LAI	long-acting injectable
LDL	low-density lipoprotein
LEN	lenacapavir

LMIC	low- and middle-income countries
LPV/r	lopinavir/ritonavir
MCH	maternal and child health
MPP	Medicines Patent Pool
NAT	nucleic acid test
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OR	odds ratio
pALD	paediatric abacavir, lamivudine, dolutegravir in a fixed dose combination tablet
PI	protease inhibitor
PLHIV	people living with HIV
PrEP	pre-exposure prophylaxis
RCT	randomized controlled trial
RMNCAH	reproductive, maternal, newborn and child and adolescent health
RNA	ribonucleic acid
RPV	rilpivirine
RR	relative risk
SOT	standard oral therapy
STI	sexually transmitted infections
TB	tuberculosis
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TLD	tenofovir + lamivudine + dolutegravir
TLE	tenofovir + lamivudine + efavirenz
TPT	tuberculosis preventive treatment
VL	viral load
WHO	World Health Organization

Acknowledgements

Co-chairs

Elaine Abrams (ICAP at Columbia University, United States of America (USA)) and **Alexandra Calmy** (Geneva University Hospital, Switzerland).

Methodologist

Roger Chou (Oregon Health & Science University, USA).

Guideline Development Group

Amgad Ali Alzahaby (Al-Azhar Faculty of Medicine, Egypt), **Moherndran Archary** (University of KwaZulu Natal, South Africa), **Pedro Cahn** (Fundacion Huesped, Argentina), **Mohamed Chakroun** (Fattouma Bourguiba Teaching Hospital, Tunisia), **Lameck Chinula** (Institute for Global Health and Infectious Diseases, Malawi), **Polly Clayden** (HIV i-BASE, United Kingdom of Great Britain and Northern Ireland (United Kingdom)), **Aleny Couto** (Ministry of Health , Mozambique), **Rosana Ditangco** (Research Institute for Tropical Medicine, Philippines), **Charles Flexner** (John Hopkins University School of Medicine, USA), **Kelly Doodley** (Vanderbilt University, USA), **Tendani Gaolathe** (Ministry of Health, Botswana), **Beatriz Grinsztejn** (Oswaldo Cruz Foundation, Brazil), **Nagalingeswaran Kumarasamy** (VHS Infectious Diseases Medical Centre, India), **Thuy Le** (Oxford University Clinical Unit, Viet Nam), **Shahim Lockman** (Bostwana-Harvard AIDS Initiative Partnership, Botswana and USA), **Imelda Mahaka** (Pangea Zimbabwe AIDS Trust, Zimbabwe), **Othoman Mellouk** (International Treatment Preparedness Coalition, Morocco), **Graeme Meintjes** (University of Cape Town, South Africa), **Lloyd Mulenga** (Ministry of Health, Zambia), **Lynne Mofenson** (Elizabeth Glaser Pediatric AIDS Foundation, USA), **Victor Musiime** (Makerere University, Uganda), **Lindiwe Mvusi** (Ministry of Health, South Africa), **Anton Pozniak** (St Stephen's AIDS Trust, United Kingdom), **Tannyawee Puthanakit** (Chulalongkorn University, Thailand), **Nini Tun** (Medical Action Myanmar, Myanmar), **Anna Turkova** (University College of London, United Kingdom), and **Francois Venter** (University of the Witwatersrand, South Africa).

External Review Group

Serge Eholie (Treichville Hospital, Cote D'Ivoire), **Antonio Flores** (Medicines sans Frontières, South Africa), **Roy Gulick** (Weill Cornell University, USA), **Diane Havlir** (University of California at San Francisco, USA), **Mariana Iacono** (Comunidad Internacional de Mujeres Viviendo con VIH (ICW), Argentina), **Andreas Jahn** (Ministry of Health, Malawi), **Karin Laine** (Posithiva Groupen, Sweden), **Valeriane Leroy** (INSERM, University of Toulouse, France), **Catia Marzolini** (University of Lausanne, Switzerland), and **Bharat B. Rewari** (Institute of Liver and Biliary Sciences (ILBS), India), **Celeste Gracia-Edwards** (The Global Fund, Switzerland).

Declarations of interest for members of the Guideline Development Group and External Review Group

No members of Guideline Development Group and External Review Group had conflicts of interest that were considered significant. Annex 1 provides details of the management of conflicts of interest.

Representatives of United Nations agencies and other partners

Carmen Pérez Casas (Unitaid, Switzerland), **Peter Ehrenkranz** (Bill and Melinda Gates Foundation, USA), **Vindi Singh** (The Global Fund, Switzerland) and **Paula Munderi** (UNAIDS, Switzerland).

Systematic review team

Lisa Abuogi (University of Colorado, USA), **Peter Bock** (Stellenbosch University, South Africa), **Jimmy Carlucci** (Indiana University School of Medicine, USA), **Andrea Cianarello** (Massachusetts General Hospital, USA), **Helen Cox** (University of Cape Town, South Africa), **Francesco Di Genaro** (Saint Camillus International University of Health Sciences, Italy), **Caitlin Dugdale** (Massachusetts General Hospital, USA), **Jessie Edwards** (University of North Carolina, USA), **Andrew Hill** (Liverpool University, United Kingdom), **Steven Kanters** (RainCity Analytics, Canada), **Giovanni Putoto** (Saint Camillus International University of Health Sciences, Italy), **Lisa Regula** (University of North Carolina, USA), **Francesco Segala** (Saint Camillus International University of Health Sciences, Italy), **Annalisa Saracino** (Saint Camillus International University of Health Sciences, Italy), **Claire Townsend** (University College of London, United Kingdom), and **Nicola Veronesi** (Saint Camillus International University of Health Sciences, Italy).

Contributors to supporting evidence and meeting presentations

Florence Anam, **Daniel Townsend** (GNP+, Kenya), **Lobna Gaayeb** (Medicines Patent Pool, Switzerland), **Jyoti Mathad** (Weil Cornell University, USA), **Sylvia LaCourse** (University of Washington, USA), **Tim Cressey** (Chiang Mai University, Thailand), **Adrie Bekker** (Stellenbosch University, South Africa), **Diana Clarke** (Boston Medical Center, USA), **Mark Mirochnick** (Boston University Chobanian and Avedisian School of Medicine, USA), **Vivian Chitiyo**, **Nicola Willis**, **Ann Sellberg** and **Tadiwanashe Nyamukuvhengu** (Zvandiri, Zimbabwe).

WHO Guideline Steering Group

Meg Doherty, **Nathan Ford**, **Morkor Newman**, **Ajay Rangaraj**, **Françoise Renaud**, **Mukta Sharma**, **Nandita Sugandhi**, **Marco Vitoria**, **Elena Vovc**, **Annabel Baddeley**, **Denis Falzon**, **Avinash Kanchar**, **Kerri Viney** (Department of HIV, TB, Hepatitis and Sexually Transmitted Infections, WHO), **Ammena Goga**, **Dube Queen** (Maternal and Child Health Programme), **Paula Munderi** (UNAIDS), **Stela Bivol** (WHO Regional Office for Europe), **Akudo Ikpeazu** (WHO Regional Office for Africa), **Kiyohiko Izumi** (WHO Regional Office for the Western Pacific), **Muhammed Jamil** (WHO Regional Office for the Eastern Mediterranean), **Po Lin Chan** (WHO Regional Office for South-East Asia) and **Omar Sued** (WHO Regional Office for the Americas).

WHO staff, consultants and interns

Wole Ameyan, **Yaa Bosomtwi** and **Ivy Kasirye** (Department of HIV, TB, Hepatitis and Sexually Transmitted Infections, WHO), **Jasmin Leuterio** (Department of HIV, TB, Hepatitis and Sexually Transmitted Infections, WHO) provided administrative support.

Overall coordination and writing

Marco Vitoria and **Elena Vovc** (Department of HIV, TB, Hepatitis and Sexually Transmitted Infections, WHO) coordinated the overall guideline development with **Nathan Ford**, **Morkor Newman**, **Ajay Rangaraj**, **Françoise Renaud** and **Nandita Sugandhi** (Department of HIV, TB, Hepatitis and Sexually Transmitted Infections, WHO) under the leadership of **Meg Doherty** (Department of Science for Health, WHO) and **Tereza Kasaeva** (Department of HIV, TB, Hepatitis and Sexually Transmitted Infections, WHO).

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Executive summary

The global HIV epidemic continues to affect nearly 40 million individuals, with over 30 million receiving treatment by the end of 2024. The effective use of antiretrovirals (ARVs) across different populations and proper management of tuberculosis (TB) and other associated conditions are essential to achieving the 2030 global elimination targets.

Significant developments in HIV treatment have occurred since the last WHO consolidated guideline was published in 2021. These include optimized use of antiretrovirals for initial and subsequent regimens, enhancing treatment safety and adherence across diverse populations. Dolutegravir (DTG)-containing regimens remain the preferred choice for initial treatment or for those failing a regimen based on a non-nucleoside transcriptase reverse inhibitor (NNRTI). For those failing DTG-containing regimens, protease inhibitors (PI) should be used as the anchor drug in subsequent regimens: darunavir/ritonavir (DRV/r) is now recommended as the preferred PI option. Tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) can be recycled in subsequent ART regimens in adults and adolescents, and abacavir (ABC) be reused in children, even if part of a previously failed treatment. This is based on improved outcomes, programmatic benefits and potential cost savings compared to switching to zidovudine (AZT) containing regimens. TAF is an alternative to TDF; the choice between TDF and TAF for adults and adolescents should be based on clinical and programmatic parameters.

New drug formulations and effective oral two-drug antiretroviral combinations are now available to simplify treatment and reduce toxicity, while bearing in mind the risks of drug resistance. Use of long-acting injectable ARVs is for the first time recommended for specific circumstances, e.g. as a switching strategy for adults and adolescents facing adherence challenges with standard three-drug oral daily regimens.

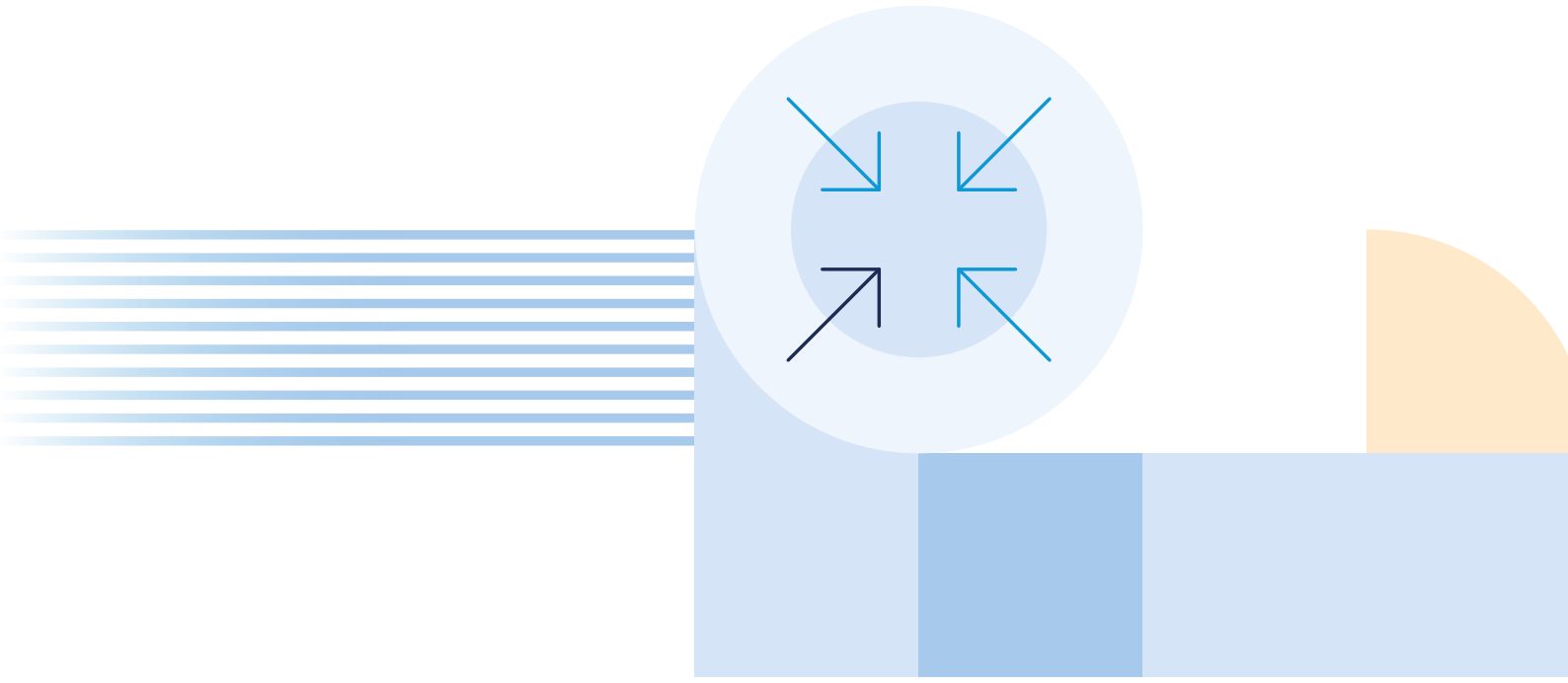
Despite significant progress in the elimination of vertical transmission of HIV and evidence that suppressive maternal ART reduces vertical transmission to an almost negligible rate, new infant infections continue to occur, particularly during the postpartum period.

The 2025 recommendations on infant postnatal prophylaxis and breastfeeding in the context of maternal HIV infection emphasize a public health approach which is centred on the well-being of both mother and infant: it supports mothers who are on ART to make an informed choice regarding breastfeeding, even in settings where national policy promotes replacement feeding. WHO continues to recommend that mothers with HIV exclusively breastfeed for the first six months, with continued breastfeeding up to 12 months and possibly up to 24 months or longer, alongside appropriate complementary feeding.

To minimize the risk of intra- or early postpartum transmission, all HIV-exposed infants should receive six weeks of single-drug prophylaxis, preferably with nevirapine (NVP). For infants of mothers who are not on ART and are at high risk of acquiring HIV, a six-week course of enhanced triple-drug prophylaxis is recommended instead of single-drug nevirapine prophylaxis. During this period the mothers should be initiated or reinitiated on ART. An extended course of single-drug prophylaxis for the infant may then be used until maternal viral suppression is assured or breastfeeding has ceased.

TB remains a leading cause of death among people living with HIV. Implementing simplified TB preventive treatment (TPT) alongside ART can significantly reduce mortality, especially with shorter TPT regimens. A new recommendation advises three months of weekly isoniazid and rifapentine (3HP) regimen as the preferred TPT option for people living with HIV, with six months of daily isoniazid (6H) and nine months of daily isoniazid (9H) regimens as alternatives based on clinical and programmatic needs. Based on clinical and programmatic considerations, other WHO recommended regimens – such as one month of daily isoniazid plus rifapentine (1HP), four months of daily rifampicin (4R), three months of daily isoniazid plus rifampicin (3HR) and six months of daily levofloxacin (6Lfx) – may be used in special circumstances. Guidance on preferential choices is based on the latest available evidence and supports a public health approach by improving adherence, simplifying care and reducing TB-related mortality; it also offers national programmes cost-effective, scalable options that integrate well with existing ART services.

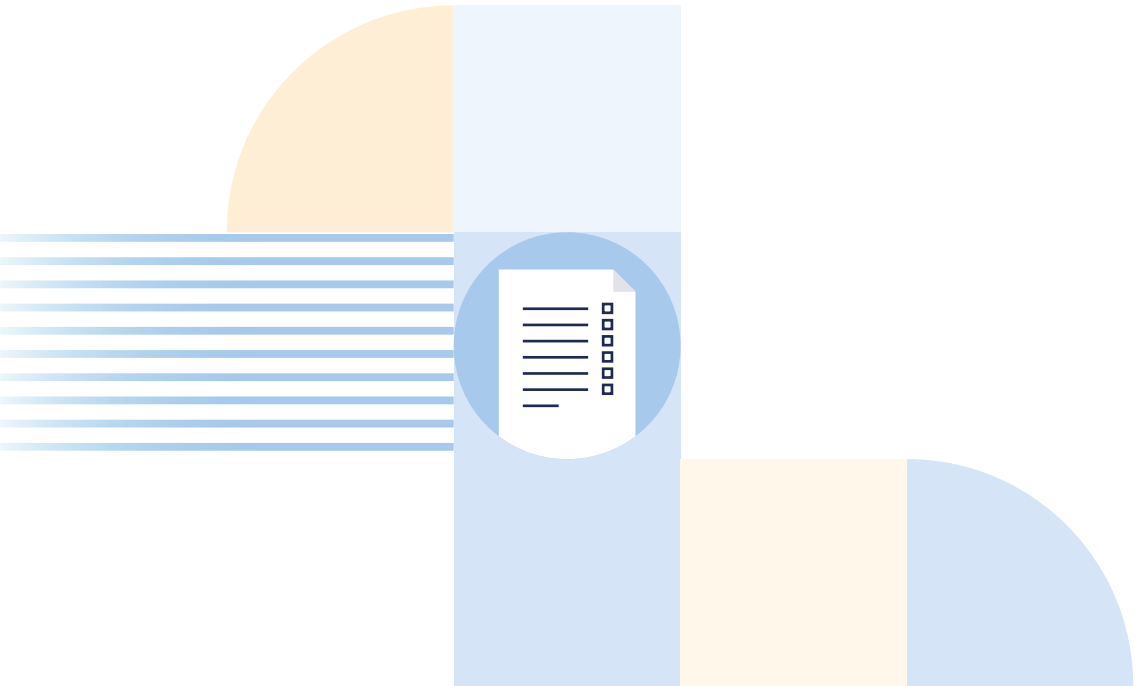
This guideline provides updated recommendations on ART, vertical transmission management and TB prevention that will be integrated within the WHO consolidated HIV guidelines in 2026. Implementing the recommendations in this guideline will impact programme priority settings, funding and service delivery. Its recommendations aim to enhance the overall effectiveness of HIV treatment and prevention strategies, expand access to care and achieve the goal of ending AIDS as a public health threat by 2030.



List of recommendations

The recommendations listed in this guideline are categorized as follows:

Existing recommendation (not changed) The recommendation was published in previous WHO guidelines. The source of the guideline is provided with the recommendation. The recommendation has not been reviewed or changed since 2021. The evidence base for the recommendation is included in the original source document, as well as in the relevant web annexes of this guideline.	Not changed
Existing recommendation (reviewed and updated) The recommendation was published in previous WHO guidelines, and evidence to inform the recommendation was reviewed for this edition. The supplementary annexes of this guideline include evidence to support the updated or replaced recommendation. The recommendation may replace/complement previous recommendations or the strength/quality evidence of the recommendation may have changed.	Updated
New recommendation The recommendation was not published in previous WHO guidelines and represents new guidance.	New



The following table summarizes all the not changed, updated and new recommendations included in this guideline, including the strength of the recommendation and certainty of the evidence.

Category	Recommendation	Strength of recommendation	Quality of evidence
Antiretroviral therapy			
Update	Darunavir/ritonavir (DRV/r) is the preferred boosted PI option for antiretroviral treatment.	Strong	Moderate
Update	Atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r) can be used as an alternative boosted protease inhibitor (PI) option for antiretroviral treatment.	Conditional	Moderate
Update	Tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) + lamivudine (3TC) or emtricitabine (FTC) is the preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone for initial and subsequent ART in adults, adolescents and children > 30 kg. This includes individuals previously treated with or exposed to tenofovir.	Strong	Moderate
Update	Abacavir (ABC) or tenofovir alafenamide (TAF) + lamivudine (3TC) or emtricitabine (FTC) is the suggested nucleoside reverse transcriptase inhibitor (NRTI) backbone for subsequent ART in children < 30 kg. This includes children previously treated with ABC or zidovudine (AZT).	Conditional	Low for ABC + 3TC Very low for TAF + 3TC (or FTC)
New	Dolutegravir (DTG) + lamivudine (3TC) can be used for treatment simplification in persons stable on 3DRs and without active hepatitis B.	Conditional	Moderate
New	Long-acting injectable cabotegravir (CAB) + rilpivirine (RPV) can be used as an alternative switching option in adults and adolescents stable on oral ART and without active hepatitis B.	Conditional	Moderate
Management of vertical HIV transmission			
Update	Infants born to mothers on ART who are not at high risk of acquiring HIV should receive six weeks of infant prophylaxis with a single drug, with nevirapine (NVP) as the preferred option. Dolutegravir (DTG) or lamivudine (3TC) are alternative options.	Strong for NVP Conditional for DTG or 3TC	Moderate for NVP Very low for DTG or 3TC
Update	Infants at high risk of acquiring HIV should receive a 3DR appropriate for age for six weeks with transition to ABC/3TC+DTG as the preferred option when available.	Strong	Low

Update	Breastfeeding infants who complete six weeks of a 3DR should follow with single-drug prophylaxis for the remainder of breastfeeding or until maternal viral suppression is achieved, with nevirapine (NVP) as the preferred option. DTG or 3TC are alternative options.	Strong for NVP Conditional for DTG or 3TC	Moderate for NVP and 3TC Very low for DTG
Not changed	In settings where the national programme recommends breastfeeding together with ARV interventions: mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (breastfeed as the general population) while being fully supported for ART adherence.	Strong	Low for 12 months Very low for 24 months
Update	In settings where the national programme recommends replacement feeding: mothers living with HIV who are receiving ART and virally suppressed should be offered the option to breastfeed and be supported in their infant feeding choice.	Strong	Low
Update	Offer enhanced community- and facility-based interventions to support mothers living with HIV who are breastfeeding in order to enhance ART adherence, improve retention of mother-and-infant pairs in care and optimize breastfeeding.	Conditional	Very low
TB prevention in people living with HIV			
New	In adults and adolescents with HIV eligible for tuberculosis preventive treatment (TPT), three months of weekly isoniazid + rifapentine (3HP) is the suggested preferred regimen; six or nine months of daily isoniazid (6H/9H) are alternative regimens.	Conditional	Low

01

Introduction

1. Introduction

Background and rationale

Almost 40 million people are estimated to be living with HIV, and over 30 million were on treatment by the end of 2024 *(1)*. Optimal use of antiretrovirals (ARVs), and simplification and harmonization of treatment guidelines remain core principles to support effective and sustainable access to treatment as well as to prevent HIV transmission. To reach the global treatment targets for ending the AIDS pandemic by 2030, innovation and optimization of ARV drug regimens and therapeutic strategies are needed.

In recent years, new drugs, new uses for existing drugs and increasing evidence of the benefits of optimized doses and formulations have emerged. Providing safe, effective and well-tolerated treatment regimens across all affected populations is essential for scaling up global treatment. Darunavir/ritonavir (DRV/r) is anticipated to be the preferred PI option for either second- or third-line regimens. Tenofovir (TDF or TAF) can be reused in second-line regimens, even if part of the failed first-line treatment. Making a choice between TDF and TAF should consider clinical and programmatic parameters, including the expanding use of TAF as an alternative to TDF. Dual regimens (oral and injecting options) may be considered in special circumstances such as simplifying treatment for people living with HIV already established on ART or for those with adherence challenges related to a standard daily oral regimen.

Rates of vertical HIV transmission remain high and without further progress to eliminate vertical transmission of HIV, the world will not achieve the 2030 global elimination goals *(2)*. While lifelong ART for all pregnant and breastfeeding women has significantly reduced transmission risk, particularly when started prior to or early in pregnancy, an increasing proportion of remaining vertical transmissions now occur during breastfeeding in the postnatal period. Although exclusive breastfeeding for the first six months of life is widely recommended as an essential practice for infant and young child health, the possibility of transmission during breastfeeding, especially when mothers are not virologically suppressed, must be addressed. Emerging data on antiretroviral use in neonatal populations highlights the need to reassess infant ARV regimens *(3)* and develop optimized postnatal prophylaxis to prevent transmission in HIV-exposed infants and young children while ensuring safe infant feeding practices.

Tuberculosis (TB) remains the primary cause of mortality among individuals living with HIV across all age groups *(4)*. The implementation of TB preventive treatment (TPT) alongside early ART initiation significantly reduces deaths due to TB among people living with HIV. To enhance TPT coverage in low- and middle-income countries (LMICs), ongoing efforts are essential. Shorter-course TPT regimens (< 6 months duration) will be an important intervention towards achieving this aim, especially if a preferred regimen is identified as most effective for those living with HIV and prioritized based on evidence from LMIC contexts. The overall benefits of TPT are anticipated to grow with the increased use of shorter rifamycin-based TPT regimens, which have shown greater safety, higher treatment completion rates and comparable efficacy to the traditional six-month isoniazid-based TPT regimens. Additional data are anticipated in 2025 to bring the use of shorter-course TPT regimens in conjunction with DTG-based regimens in pregnant women and children up to date.

This guideline provides updated and new recommendations on antiretroviral therapy, management of vertical HIV transmission and TB prevention in people living with HIV. The recommendations developed for this document will be integrated with the updated consolidated HIV guideline to be released in the second half of 2025. The following paragraphs outline the rationale for including these topics in the guideline.

Antiretroviral therapy

Since 2013, WHO's consolidated ART guidelines have promoted treatment optimization by standardizing and simplifying ART strategies across programmes, promoting the use of once-daily regimens to improve convenience and rapidly updating guidance for first-line ART based on safer and more effective treatments. More recently, the development of long-acting ARV drug formulations now has the potential to improve treatment adherence and sustain viral suppression. At the same time, the introduction of new drug classes and emerging evidence of the clinical and programmatic benefits of optimized dosing and formulations of existing drugs provide a rationale for periodic assessment of WHO drug selection and sequencing treatment strategies for future normative revisions.

Successful scaling up of paediatric ART means that more infants and young children with previous exposure to an array of ARV drugs are surviving into adulthood and require effective treatment options in the face of drug resistance. As the cohort of people living with HIV ages, challenges related to polypharmacy and adverse events of concern among ageing populations are also anticipated to become more important.

Tenofovir alafenamide (TAF) is a prodrug formulation of tenofovir, and some comparative studies have suggested that it can lead to less impact on bone mineral density and renal function laboratory markers than tenofovir disoproxil fumarate (TDF). Since the last major guideline update, more safety data on TAF in specific populations – such as pregnant women, children and people living with hepatitis B coinfection – and more information on body weight gain and the cardiometabolic impact of TDF and TAF has become available. Additionally, TAF leads to fewer discontinuations due to kidney-related side-effects when used with boosted protease inhibitors (PI) compared to TDF.

Current WHO recommendations on the use of DRV/r were established in 2013: DRV/r was considered an alternative PI option in second-line ART and a preferred PI option in third-line ART. Since these WHO recommendations were published, there has been a large programmatic transition to dolutegravir (DTG), both as first- and second-line option. New data from large clinical studies in adults have been published, presenting direct comparisons between DRV/r and other PIs; additional – if limited – data are available for paediatric populations. Generic co-formulations of DRV/r 400/50 mg have become available at reduced cost that can conveniently provide a once-daily DRV/r 800/100 mg dose in adults and adolescents.

Studies increasingly support switching from tenofovir + lamivudine + efavirenz (TLE) to tenofovir + lamivudine + dolutegravir (TLD) regardless of viral load, with minimal drug resistance observed *(5)*. This shift reflects a change in the paradigm of ART sequencing, especially in a post-DTG transition era, where most individuals are now on TLD but have varied ART histories. This is especially relevant for people with vertically acquired HIV, who have probably been exposed to a mix of optimal and suboptimal regimens throughout their lives.

Another recent topic in ART optimization is the use of dual antiretroviral combinations (both oral and injectable) as a simplification strategy for adults on established ART or for those with adherence challenges. The potential advantages of dual regimens must be weighed against concerns, particularly regarding the increased risk of drug resistance, coinfection management (e.g. hepatitis B), and the lack of studies in LMICs. Recent clinical and programmatic studies – including the use of long-acting injectables for adolescents and adults – are expanding the evidence base, with ongoing work to establish dosing for paediatric populations.

Managing vertical HIV transmission

To reduce the risk of vertical transmission, initiating infant ARV prophylaxis at birth remains a key strategy for HIV prevention. Despite expanded maternal ART coverage and improved viral suppression rates with newer DTG-based regimens, vertical transmission during the breastfeeding period persists, contributing to a greater proportion of new infant infections now occurring during the postnatal period, even when coverage of ART during pregnancy remains high.

WHO's 2016 guidance for HIV-exposed infants included recommendations for managing neonates with HIV infection during the first month of life, alongside guidance to consider birth testing to detect in utero infections. Early treatment in the neonatal period has been shown to significantly reduce mortality in the first two months and limit the establishment of viral reservoirs *(3)*. Since these recommendations, there has been an increase in the availability of new ARV formulations and a growing interest in developing ARV options suitable for young infants.

Since the 2016 recommendations, WHO has also advised that routine prophylaxis should be provided to all HIV-exposed infants: six weeks of nevirapine (NVP) or six weeks of zidovudine (AZT) for those receiving replacement feeding after delivery. For high-risk infants, intensified prophylaxis with a combination of AZT and NVP is recommended for the first six weeks, followed by an additional six weeks of either both drugs or NVP alone. More potent regimens that rapidly reduce viral load have since become widely available and are safe for use during pregnancy and breastfeeding, but a clear approach is needed when maternal HIV infection or viraemia is identified after delivery and during breastfeeding. Breastfeeding is universally recognized for neonatal survival and maternal and child health, benefiting both throughout their lives. Maternal ART with viral suppression and infant ARV prophylaxis are crucial interventions that can significantly reduce vertical transmission of HIV during breastfeeding to almost negligible levels. By introducing more potent and safer regimens for pregnant and breastfeeding women, coupled with effective early infant treatments, updated guidelines contribute to reducing vertical transmission and improving infant survival rates through early diagnosis and treatment. However, interventions are still required to ensure that the risk of vertical transmission in the postpartum period is minimized.

Previous WHO guidance lacked specific recommendations for managing infants identified at risk of vertical transmission during the breastfeeding period. This is particularly critical when viraemia may occur due to maternal infection after delivery, missed prenatal diagnoses, inadequate antenatal care, suboptimal viral load monitoring or insufficient maternal drug levels. Although maternal ART has been scaled up during pregnancy, postnatal infections account for an increasing proportion of those vertical transmissions that still occur. The late recognition of HIV exposure presents challenges for health workers, especially those without paediatric expertise or access to referral systems. Furthermore, as recommended drugs for infants are part of an increasingly fragile paediatric ARV market, reviewing the available evidence in infant postnatal prophylaxis has become crucial in order to support data-driven decisions and inform ARV manufacturers about products that will remain essential to prevent future vertical transmission of HIV or to provide early treatment for those acquiring HIV infection.

Tuberculosis prevention in people living with HIV

Tuberculosis preventive treatment (TPT) in people living with HIV is a crucial element of WHO's global health sector strategies on HIV, hepatitis and STIs, as well as the global End TB strategy. In 2020, WHO recommended shorter rifamycin-based regimens for global scale-up along with other TPT regimens based on evidence from randomized controlled trials (RCTs) supporting the efficacy of shorter treatments. These recommendations are applicable to different populations at risk, including people living with HIV. The TPT guidelines were updated in 2024 and recommend TPT options such as six or nine months of daily isoniazid (6H/9H) or three months of weekly isoniazid + rifapentine (3HP) or three months of daily isoniazid +rifampicin (3RH) for all eligible persons regardless of HIV status; one month of daily isoniazid + rifapentine (1HP) or four months of daily rifampicin (4R) may be used as alternative regimens.

Recommending optimized, preferential TPT regimens for people living with HIV can streamline service delivery, reduce costs and improve health outcomes. This mirrors principles used in ART optimization that led to success in the public health approach to the HIV response aiming at ART scale-up and increasing treatment coverage: standardization, simplification and strategic prioritization based on efficacy, feasibility and patient preference.

In view of the increasing availability of rifapentine-based TPT shorter regimens, recent evidence on the safe co-administration of DTG and the need to scale up TPT in people living with HIV in LMICs, there is a strong rationale for prioritizing and recommending a preferential, more effective TPT regimen for adults and adolescents living with HIV in order to benefit from the potential gains of treatment optimization under a public health approach.

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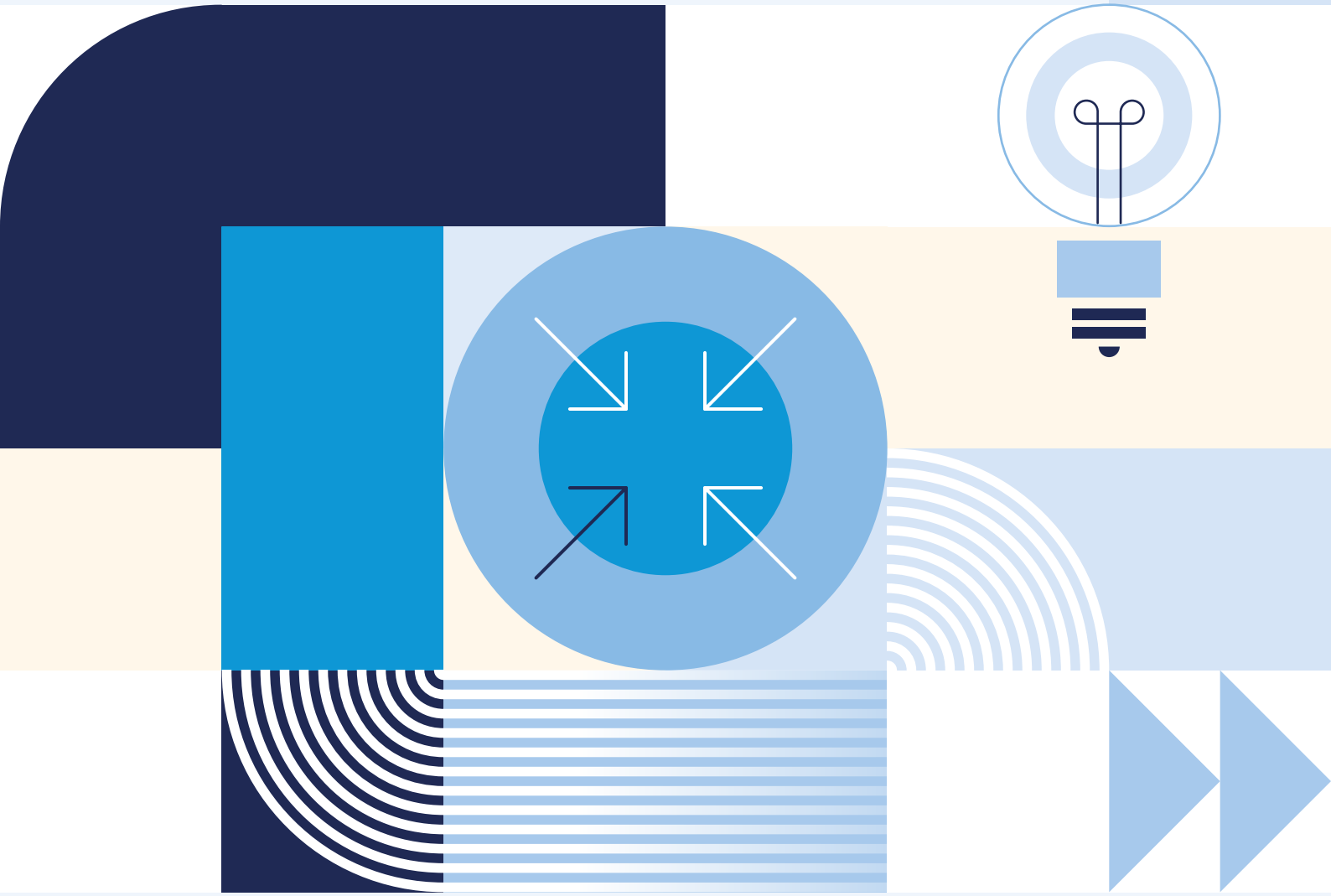
* All references were accessed on 11.11.2025

02

Objectives, desired impact, target audience and guiding principles of the guideline



2. Objectives, desired impact, target audience and guiding principles of the guideline

2.1 Objectives

The objective of this guideline is to provide updated evidence-based recommendations on the following points:

- optimal use of antiretroviral drugs and treatment strategies in all individuals living with HIV whether adults, adolescents, pregnant women or children;
- optimal guidance on infant ARV prophylaxis at birth and safe breastfeeding practices to reduce the risk of vertical HIV transmission during pregnancy, labour and the breastfeeding period; and
- optimal guidance on the preferential tuberculosis preventive treatment (TPT) regimen in people living with HIV.

2.2 Desired impact

The desired impact is to reduce the mortality, morbidity and transmission of HIV, leading to fewer cases of HIV and TB transmission and HIV virological failure, and thereby easing the pressures on health care systems.

2.3 Target audience

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

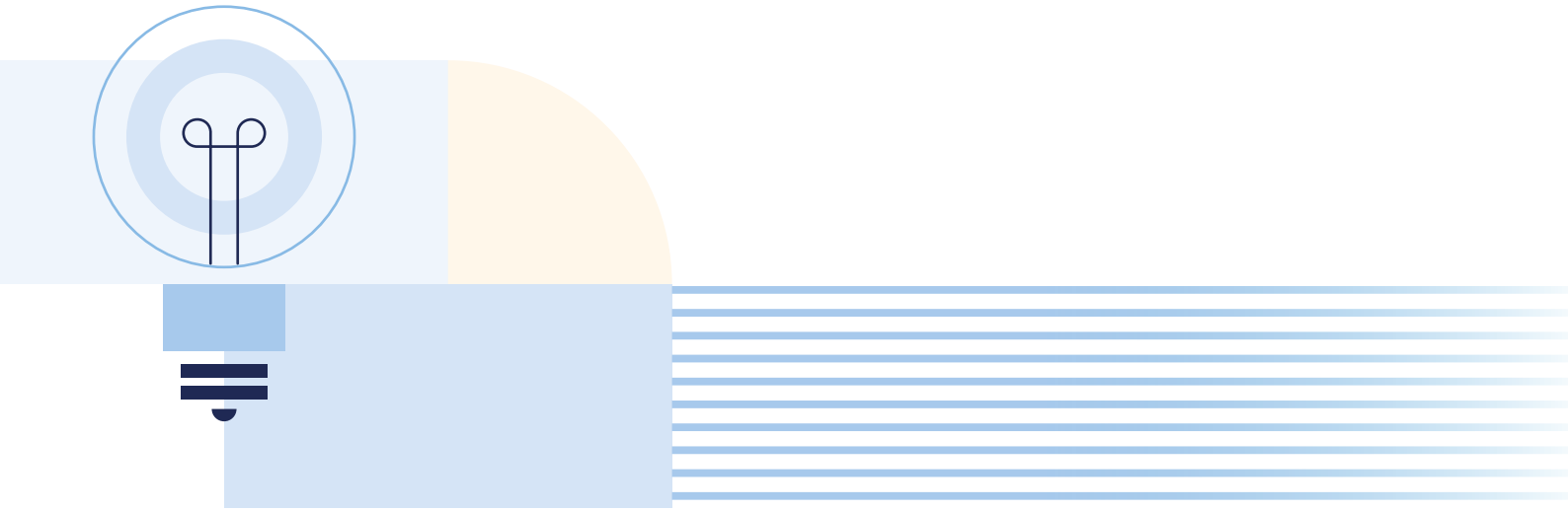
- people living with HIV and community-based organizations;
- national HIV treatment and prevention advisory boards;
- clinicians and other health workers;
- managers of national laboratory services;
- civil society organizations; and
- international and bilateral agencies and organizations that provide financial and technical support to HIV programmes in resource-limited settings

2.4 Guiding principles

The following principles have prevailed in the development of this guideline and should guide how its recommendations are put into practice.

- To contribute to the Sustainable Development Goals by achieving key global and national HIV goals.
- To adopt a public health approach for scaling up the use of ARV drugs and other therapeutic agents along the continuum of HIV prevention, care and treatment.
- To encourage additional efforts to promote and protect the human rights of people who need HIV services, with full and accurate provision of information on the benefits and risks of health interventions in a non-judgemental and culturally adequate language in order to prevent stigma and discrimination and promote gender equity.
- To promote a person-centred approach to health care that consciously adopts the perspectives of people living with HIV and their families and communities, with care and services provided in ways that respect patient autonomy in decisions made about their health and offer options to enable patients to make informed choices.
- To embrace a human rights-based approach and take into account local context, including HIV epidemiology, availability of resources, health system organization and capacity and anticipated cost-effectiveness.

Annex 1 describes the methods for developing this guideline.



03

Optimization of antiretroviral therapy

3. Optimization of antiretroviral therapy

3.1 Use of darunavir/ritonavir and other protease inhibitors in HIV treatment

3.1.1 Recommendations

Recommendations 2025

Darunavir/ritonavir (DRV/r) is the preferred boosted protease inhibitor option for antiretroviral treatment.
strong recommendation, moderate certainty of evidence

Atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r) can be used as an alternative boosted protease inhibitor for antiretroviral treatment.
conditional recommendation, moderate certainty of evidence

3.1.2 Background

According to the 2019 WHO guideline, boosted protease inhibitors (PI), in combination with a nucleoside reverse transcriptase inhibitor (NRTI) backbone, are currently recommended as the preferred subsequent regimen for individuals living with HIV whose dolutegravir (DTG)-based regimens are failing *(1)*. However, the evidence supporting a preferred PI option was unclear. The systematic review and network meta-analysis conducted in support of the 2019 guideline found no significant differences between atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r) and lopinavir/ritonavir (LPV/r) *(2)*. High cost and lack of generic formulations were also barriers to recommending DRV/r as a preferred option *(3)*.

Since publication of the 2019 guideline, new data from large clinical studies have provided direct comparisons between DRV/r and other PIs *(4–6)*. More recently, generic formulations of DRV/r have become available at reduced costs *(7)*. A WHO technical report published in October 2024 indicated that the adoption of DRV/r for HIV treatment in national guidelines has increased in LMICs, and that there is a trend towards recommending it as an alternative or even preferred PI option *(3)*. Drug demand forecasting suggests that approximately 7–8% of individuals receiving ART are currently using a PI-based regimen, with projections showing a progressive decrease in the use of LPV/r and an increase in the use of DRV/r in the coming years *(8)*.

Comparative studies on PIs in pregnant and breastfeeding women are limited, with clinical guidelines differing on dosing schedules for DRV/r (once daily versus twice daily), especially during late pregnancy *(9,10)*.

In children, the use of DRV/r remains limited because no formulation is currently available. The Unitaid and the Clinton Health Access Initiative have partnered with a generic producer to accelerate the development of a DRV/r formulation for children, which should become available in the near future *(11)*.

3.1.3 Supporting evidence

Use of darunavir/ritonavir as preferred protease inhibitor in adults and adolescents with HIV

A systematic review and network meta-analysis conducted for the guideline identified 11 clinical trials *(12–49)*; this evidence was further supported by noncomparative studies from eight clinical trials comparing the use of PIs in adults and adolescents *(51–69)* for initial therapy. Assessed efficacy outcomes included viral suppression, CD4 cell count changes and mortality. Safety and tolerability outcomes included the risk of adverse events and treatment discontinuation. The network meta-analysis demonstrated that among PI options, DRV/r and ATV/r have comparable rates of viral suppression at 96 weeks (OR=1.08; 95% credible interval [CrI]: 0.84–1.41), and these are better than LPV/r (DRV/r: OR=1.50; 95% CrI: 1.14–1.96) (ATV/r: OR=1.38; 95% CrI: 1.08–1.77). DRV/r showed a slight trend toward lower CD4 cell count gains when compared to LPV/r, but these differences were small and not statistically significant (and based on a single study).

DRV/r and ATV/r exhibited similar risks of treatment discontinuation (OR=1.04; 95% CI: 0.83–1.30), both outperforming LPV/r (DRV/r: OR=0.57; 95% CrI: 0.29–1.05) (ATV/r: OR=0.70; 95% CrI: 0.55–0.89). However, DRV/r had an overall better safety profile, showing lower occurrence of adverse events compared to both ATV/r (OR=0.43; 95%CrI: 0.33–0.55) and LPV/r (OR=0.39; 95% CI: 0.27–0.55). DRV/r was associated with higher blood lipid levels than ATV/r but posed a lower risk of hyperbilirubinaemia, which is a common adverse event associated with ATV/r. LPV/r was associated with less weight gain compared to both ATV/r and DRV/r.

The overall certainty of the evidence regarding the desirable and undesirable effects for adults and adolescents was rated as moderate when comparing DRV/r with LPV/r, and low when comparing DRV/r with ATV/r (mostly due to the indirect nature of the evidence).

Use of darunavir/ritonavir as preferred protease inhibitor in pregnant and breastfeeding women with HIV

A systematic review and network meta-analysis incorporated evidence from 15 studies conducted in pre- and post-conception populations. Most data came from observational studies, using different NRTI backbone drugs *(69–93)*.

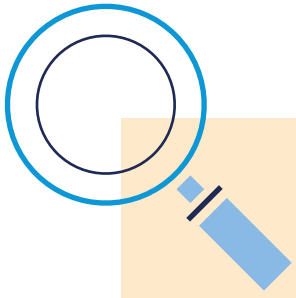
DRV/r and ATV/r were comparable in terms of rates of virological suppression (+8.11%; 95% CrI: -11.45 to +27.39%), but there was a higher likelihood of viral suppression in pregnant women on DRV/r-based regimens when compared to LPV/r (+20.61%; 95% CI: 1.4 to 40.61%). DRV/r and ATV/r were also comparable in terms of safety, but there was a trend towards a higher risk of negative pregnancy outcomes, preterm births and small-for-gestational-age births among women receiving LPV/r-based regimens.

Overall, the available evidence indicates that, as observed in the general adult and adolescent population living with HIV, DRV/r has favourable safety and viral efficacy in pregnancy, with some evidence for the superior viral efficacy of DRV/r when compared to LPV/r. However, the certainty of evidence regarding the desirable and undesirable effects for pregnant women in this review was rated as low to very low, mainly because the studies were at high risk of bias.

The optimal DRV/r dosing schedule (once daily vs twice daily) during pregnancy is unclear (see Section 3.1.4).

Use of darunavir/ritonavir as preferred protease inhibitor in children with HIV

For the paediatric population, the systematic review included two randomized clinical trials which showed that DRV/r was superior to ATV/r or LPV/r (OR=1.98; 95% CI: 1.38–2.90) in achieving viral suppression *(94–100)*. As with adults, DRV/r had a better overall safety profile among the boosted PI options, with a low-to-moderate risk of grade 3 and 4 adverse events when compared to ATV/r and LPV/r. The overall certainty of evidence regarding the desirable and undesirable effects for children in this review was rated as moderate.



3.1.4 Rationale for the recommendation

Balance of effects

For non-pregnant adults and adolescents with HIV, the overall balance of benefits to harms favours DRV/r compared to ATV/r, based on similar effects on efficacy but decreased harms (including decreased occurrence of severe adverse events and the risk of hyperbilirubinaemia). The overall balance of benefits to harms also favours DRV/r compared to LPV/r, based on improved efficacy (higher viral suppression) and decreased harms (lower risk of any adverse events). For pregnant women, the evidence appears to favour DRV/r compared to other PIs (increased likelihood of viral suppression with no clear differences in adverse pregnancy outcomes). Among children, the evidence favours DRV/r compared to other PIs (increased likelihood of viral suppression and decreased risk of grade 3 and 4 adverse events).

Values and preferences

A values and preferences survey conducted for this guideline confirmed that people living with HIV prefer antiretroviral regimens that are effective even with partial drug resistance. They also prefer once-daily fixed-dose combinations with minimal side-effects and little interference with diet or other medications. They value not being exposed to side-effects such as skin rash, jaundice, body weight changes and long-term negative effects on bone, renal and cardiometabolic health.

Overall, the Guideline Development Group determined that DRV/r is associated with similar or slightly increased benefits and fewer harms across populations, when compared to ATV/r and LPV/r. Deciding to choose DRV/r over other PIs may therefore not be sensitive to variability in preferences regarding outcomes for most patients. However, there are some potential trade-offs with using DRV/r (e.g. dyslipidaemia) or advantages (less hyperbilirubinaemia) that could impact decisions for some patients.

Cost and cost-effectiveness

In recent years, the price of DRV/r has decreased with the development of generic DRV/r formulations *(101)*. However, despite this price reduction, DRV/r is still more expensive than ATV/r although DRV/r is slightly cheaper than LPV/r in LMICs *(102)*. With the promotion of additional economies of scale, the price of DRV/r is expected to further decrease. However, some upper middle-income countries cannot access the cheaper generic DRV/r formulations due to patent and licensing restrictions.

For children, generic formulations are still under development. The current DRV/r paediatric formulations (available as separate tables) cost significantly more than paediatric LPV/r formulations.

In pregnant women, the DRV/r cost will be influenced by the dose schedule used: if DRV/r is used at a dose of 800/100 mg once daily it will be similar to adults and adolescents; if DRV/r is used at a dose of 600/100 mg twice daily, the cost will be higher (see Section on implementation considerations).

DRV/r is more cost-effective than LPV/r due to better tolerability and efficacy. A study in a high-income setting shows that DRV/r is a cost-effective PI component, although this study examined nongeneric formulations *(103)*. Limited studies have evaluated the cost-effectiveness of PIs using generic co-formulations in LMICs. Most studies have focused on salvage treatment strategies or used higher DRV/r prices in their analysis compared to what is currently available *(104)*. A recent model suggested that replacing LPV/r and ATV/r with generic DRV/r and DTG can be cost-effective in resource-limited settings, improving health outcomes and saving costs *(105)*.

Acceptability and equity impact

The overall acceptability of DRV/r as a preferred PI is well supported by people living with HIV and health care providers due to its good safety and tolerability profile and high efficacy in all populations when compared to other PI options. Other factors supporting acceptability include availability of a once-daily co-formulation for adults and adolescents and comparable affordability *(106)*.

The provision of a more effective and safer PI option could also increase equity, assuming that options are available, accessible and affordable to all who could benefit. However, some potential cost and access barriers could exacerbate health inequalities for rural and marginalized populations. Access to generic DRV/r formulations can be limited in some countries due to patent barriers.

Feasibility

Darunavir is registered in many countries, with several suppliers manufacturing generic formulations and able to work at full capacity to cover increased demand. Programmatic rollout of generic DRV/r use in several LMICs has been demonstrated, with early involvement of community groups and improved uptake and transition *(107)*. For these reasons, the Guideline Development Group considered that implementing DRV/r is feasible and can be successfully integrated into national HIV treatment programmes.

Conclusions

The Guideline Development Group strongly recommend DRV/r as the preferred PI option when a PI is used, based on the moderate certainty of evidence of increased benefits and reduction in harms, low comparative cost difference, high acceptability and positive equity impact compared to other PI options. As a result, the previous recommendations for the use of ATV/r and LPV/r have been conditionally downgraded to preferred alternative options. **Table 3.1** provides a comparison of major clinical and programmatic parameters for these regimens.

3.1.5 Implementation considerations

The implementation of DRV/r as a preferred PI option for adults and adolescents has been demonstrated in several national HIV treatment programmes in LMICs, particularly with the development of generic formulations. However, its use can be limited or contraindicated in certain clinical situations or specific populations, and alternative PI options should be available.

As observed with other PIs, the use of DRV/r in people with HIV-associated TB coinfection has limitations due to pharmacological drug interactions with rifampicin, which significantly reduce DRV/r levels. Increased doses of DRV/r (1600/200 mg once daily or 800/100 mg twice daily) could potentially overcome this drug level reduction but significantly elevate the risk of hepatotoxicity *(108)*. The concomitant use of rifampicin and LPV/r with dose adjustment (800/200 mg twice daily or 400/400 mg twice daily) is also associated with a high incidence of hepatic adverse effects *(109)*. More recently, a pharmacokinetic study with a small number of people living with HIV showed that a double dose of ATV/r (300/100 mg twice daily) was able to overcome the interaction with rifampicin given at a dose of 600 mg once daily without subsequent significant elevation of liver enzymes or rebound viraemia *(110)*. Rifabutin can replace rifampicin when used with ATV/r or DRV/r, but it is more expensive, requires dose adjustments and toxicity monitoring, and has limited availability *(111)*.

DRV/r-based ART is widely considered safe and effective for use during pregnancy. However, pharmacokinetic studies have reported reduced drug exposure during the later stages of pregnancy, prompting ongoing discussion about the optimal dosing strategy – specifically, once-daily versus twice-daily administration *(112)*. An analysis of observational data carried out by the WHO Pregnancy Therapeutics Working Group found that once-daily DRV/r 800/100 mg is effective in achieving viral suppression during pregnancy *(113)*. Given the potential for reduced drug concentration with once-daily dosing during late pregnancy, routine viral load monitoring remains essential.

DRV/r cannot be used in children under three years old or weighing less than 10 kg due to insufficient pharmacokinetic data and potential toxicity *(114)*. For children older than three years, dose adjustments based on the child's weight and age are necessary, and the availability of appropriate co-formulations of DRV/r for children remains a challenge. Liquid formulations may be available but are often unpalatable for children and require separate ritonavir for boosting. Tablet formulations are not feasible for younger children who cannot swallow pills, and current originator formulations require separate ritonavir for boosting effect. A heat-stable DRV/r 120/20 mg tablet for children is awaiting regulatory approval and has been recently reviewed and endorsed by the WHO Paediatric ARV Working Group *(115)*.

3.1.6 Research gaps

For adults and adolescents, studies are needed on the long-term efficacy and safety of DRV/r in treatment-experienced individuals, including elderly people and those with drug-resistant HIV or chronic comorbidities. It is important to monitor the outcomes of switching to DRV/r-based regimens from other antiretroviral therapies, particularly in virologically suppressed patients. Investigations examining simplified combinations of DRV/r with other ARVs (such as DTG) to improve treatment outcomes and reduce pill burden are also encouraged.

More research is needed on the safety and efficacy of higher doses of ATV/r with rifampicin in HIV-associated TB coinfection.

For pregnant and breastfeeding women, surveillance of pregnancies in women receiving DRV/r once daily is required to provide further evidence supporting the use of this dosing schedule in pregnant women, particularly in the third trimester. Further studies focused on understanding the pharmacokinetics of DRV/r during pregnancy to ensure adequate drug exposure and viral suppression are important. Ongoing studies assessing the long-term safety of DRV/r during pregnancy, including the risk of congenital anomalies, pregnancy and birth outcomes, are also necessary.

For children, finalizing the development and evaluation of paediatric formulations of DRV/r to ensure appropriate dosing and ease of administration is critical. Research on the pharmacokinetics, safety and efficacy of DRV/r in children, particularly those failing initial therapy, is needed. Implementation studies investigating the use of DRV/r in paediatric populations living in LMICs, focusing on accessibility and adherence, are also essential.

Table 3.1 Comparison of atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r) and lopinavir/ritonavir (LPV/r)

Major parameters	ATV/r	DRV/r	LPV/r
Consistency with paediatric regimens	Yes[a]	Yes[b]	Yes
Number of pills per day (standard dose as co-formulation)	1	1–2	4
Convenience (once daily versus twice daily)	Once daily	Once or twice daily[c]	Twice daily
Safety in pregnancy	Yes	Yes	Yes[d]
Gastrointestinal intolerance	±	±	++
Availability as adult generic co-formulations	Yes	Yes	Yes
Availability as paediatric generic co-formulations	No	No[e]	Yes[f]
Hyperbilirubinaemia	++	-	-
Dyslipidaemia	±	+	+
Accessibility in LMICs	High	Moderate	High

ATV/r = atazanavir/ritonavir; DRV/r = darunavir/ritonavir, LPV/r = lopinavir/ritonavir, LMICs = low- and middle-income countries, PLHIV = people living with HIV

a. ATV/r can replace LPV/r for children over three months old but consider limited availability of formulations for those under six years of age, lack of fixed dose and separate ritonavir booster administration.

b. DRV/r is not approved for children under three years of age.

c. In PLHIV failing on a PI-containing regimen, DRV/r should be used in a higher dose (600/100 mg twice daily) in the subsequent regimen.

d. LPV/r is associated with occurrence of more pregnancy adverse outcomes than ATV/r and DRV/r.

e. A generic DRV/r paediatric formulation (120/20 mg) is under final development.

f. LPV/r syrup or granules can be used if starting after 2 weeks of age.

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3.2 Use of tenofovir and abacavir for initial and subsequent regimens in HIV treatment

3.2.1 Recommendations

Recommendations 2025

Tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) + lamivudine (3TC) or emtricitabine (FTC) is the preferred nucleoside reverse transcriptase inhibitor (NRTI) backbone for initial and subsequent ART in adults, adolescents and children > 30 kg. This includes individuals previously treated with or exposed to tenofovir or zidovudine (AZT).
strong recommendation, moderate certainty of evidence

Abacavir (ABC) or tenofovir alafenamide (TAF) + lamivudine (3TC) or emtricitabine (FTC) is the suggested nucleoside reverse transcriptase inhibitor (NRTI) backbone for subsequent ART in children < 30 kg. This includes children previously treated with ABC or zidovudine (AZT).
conditional recommendation, low certainty of evidence for ABC+3TC, very low certainty of evidence for TAF+3TC (or FTC)

3.2.2 Background

Since 2013, WHO has recommended switching the backbone to zidovudine (AZT) + lamivudine (3TC) if tenofovir disoproxil fumarate (TDF) + 3TC is failing, and vice versa *(1)*. In an interim review conducted in 2018, data emerged in support of maintaining the backbone regimen and changing only the anchor drug: switching to dolutegravir (DTG) in combination with TDF+3TC (TLD) for people for whom efavirenz in combination with TDF+3TC (TLE) has failed *(2)*.

TLD has become the standard of care worldwide, with high rates of viral suppression *(3)*. Several clinical and observational data support switching from TLE to TLD regardless of the HIV viral load (i.e. without viral load testing), with low levels of drug resistance development *(4–6)*. This has led to a change in the paradigm of antiretroviral regimen sequencing: most people have started on or been switched to TLD, irrespective of their exposure to prior treatment regimens.

In mid-2023, WHO updated the HIV viral load monitoring algorithm, including the timing of the first viral load, timing of the repeat viral load after an elevated viral load, treatment failure threshold and immediate (i.e. after single viral load) regimen switch if a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen fails *(7)*.

Another important change has been the accumulation of safety data for tenofovir alafenamide (TAF) as an alternative to TDF *(8–11)*. According to the latest WHO estimates, about 200 000 people living with HIV used TAF in LMICs in 2023, mainly in the WHO African Region and Region of the Americas *(12)*. There is little evidence about how TDF or TAF work with boosted PI regimens in LMICs but now that the use of second-line regimens including boosted PI is expected to increase, it is important to understand the safety of TDF and TAF in these situations.

3.2.3 Supporting evidence

Recycling tenofovir in nucleoside reverse transcriptase inhibitor (NRTI) backbones for adults and adolescents with HIV

Systematic review identified 13 studies evaluating TDF-recycling strategies in adults and adolescents. Eligible studies included direct evidence comparing TDF recycling to AZT switch (five studies) (13–19], studies comparing partially versus fully active NRTIs (five studies) *(20–24)* and supportive evidence from noncomparative trials (three studies) *(5, 25–27)*.

The most direct evidence comes from the NADIA trial, which was designed to specifically answer this question *(13,16)*. This trial demonstrated that at 96 weeks, adults and adolescents failing an initial regimen who maintained TDF in the subsequent regimen had better viral suppression (+7% [95% CI: 1.2–12.8%]) and CD4 cell count increase (+59 cells/mm3 [95% CI: 18–100 cells/mm3]) compared to those who switched to AZT. This advantage remained consistent across various subgroups, including those with TDF resistance mutations. Recycling TDF was associated with fewer grade 3 and 4 adverse events and decreased risk of resistance, but with imprecise estimates. Among those who developed DTG resistance, five out of seven were on AZT, suggesting that switching to AZT may increase the risk of DTG resistance among those who do not achieve or maintain viral suppression. Regarding the occurrence of discontinuations and weight changes and body mass index, both recycling and switching were comparable, but estimates were imprecise *(31)*.

Three additional studies – ARTIST, D2EFT and VISEND – provided supporting evidence *(25–27,29–30)*. ARTIST is a single-arm study that showed high levels of viral suppression among patients using TLD following failure of a TDF-containing NNRTI-based regimen *(26,29)*. ARTIST also showed that no patient with recycled TDF developed DTG resistance. D2EFT and VISEND compared TLD to boosted PI with optimized or AZT-switched NRTI backbones but could not disaggregate the effects of TDF recycling from DTG *(25,30)*. Nonetheless, both studies found that TLD was noninferior to boosted PI with optimized NRTI backbone, with VISEND finding statistically superior viral suppression with TLD *(30)*.

Evidence favouring TDF recycling instead of switching to AZT was further supported by several observational studies which demonstrated a higher probability of viral suppression among people maintaining tenofovir in subsequent regimens *(14,15,17–19,23,24,32,33)*.

The certainty of evidence on the effects of virological suppression and changes in CD4 cell counts for adults and adolescents failing first-line treatment who maintained tenofovir in the subsequent regimen was rated as moderate. For other outcomes, the certainty of evidence was rated as low.

Recycling abacavir in nucleoside reverse transcriptase inhibitor (NRTI) backbones in children with HIV

Direct evidence on outcomes associated with ABC recycling versus switching to AZT is not available. Evidence from two studies (CHAPAS-4 and ODYSSEY) found ABC associated with a decreased likelihood of virological failures versus AZT at 96 weeks (OR=0.55; 95% CI: 0.40–0.75) *(34–40)*. However, these trials did not randomize children to ABC or AZT (they were designed to evaluate other randomized comparisons) and rates of switching and recycling were not reported. In both studies, children with high or intermediate resistance to ABC were less likely to experience virological failure than those using AZT (OR=0.24; 95% CI: 0.11–0.54). Additional analyses of four longitudinal cohorts examined risk factors associated with the emergence of DTG-based resistance mutations and found that DTG resistance was significantly lower with ABC compared to AZT (OR=0.18, among patients with genotyping; 95% CI: 0.05–0.62) *(41)*. Altogether, these data suggest that ABC use in children was associated with a lower risk of virological failure and DTG resistance than AZT.

The certainty of evidence on virological suppression effects in children failing first-line treatment who continued on ABC in the subsequent regimen was rated as low, given the lack of evidence directly comparing ABC recycling versus AZT switching. For DTG resistance risk, the certainty of evidence was rated as very low, due to the risk of bias and indirectness.

Use of tenofovir alafenamide in adults, adolescents and children with HIV

The systematic review and metanalysis included 11 randomized clinical trials conducted in adults and adolescents that compared TAF- and TDF-based regimens for at least 24 weeks *(42–52)*. Subgroup analyses were performed to assess whether there were differential effects based on the use of boosted (i.e. containing low-dose ritonavir) or unboosted (i.e. not containing low-dose ritonavir) regimens.

Overall, there was no difference in viral suppression between unboosted TAF- and TDF-containing regimens (RR=1.00; 95% CI: 0.96–1.04). Boosted TDF-containing regimens showed a slightly higher rate of viral suppression compared to boosted TAF-containing regimens (RR=1.03; 95% CI: 1.01–1.04), although the absolute difference was small (1%; 95% CI: 1–1%). No difference in viral suppression was observed in pregnant women, but the evidence is limited (one study) *(45)*. There was no significant difference in mortality: results were very imprecise since the trials were not designed to assess this outcome.

Regarding safety outcomes, there were no significant differences between TAF and TDF for grade 3 and 4 adverse events, severe adverse events and occurrence of bone fractures. No differences were seen between boosted and unboosted subgroups. Renal adverse events (renal tubule adverse events, discontinuations due to renal events) were rare and showed a small but statistically significant difference favouring boosted TAF over boosted TDF regimens (renal tubule adverse events RR=0.17; 95% CI: 0.04–0.84; discontinuations due to renal dysfunction RR=0.19; 95% CI: 0.06–0.55); no events were documented in unboosted regimens. The decline in renal function (measured by eGFR) was lower with TAF than TDF in all seven trials reporting this outcome, but the absolute difference was small (mean difference range: -2.3 to -7.7 mL/min/1.73m2). Rise in total cholesterol was greater with TAF than TDF in all 10 studies reporting the outcome, but the absolute difference for this outcome was also small (mean difference range: +13 to + 35 mg/dL).

Pregnancy adverse events were evaluated in one trial (VESTED study), and fewer adverse pregnancy, maternal and child outcomes (preterm delivery, small for gestational age infant, stillbirth or infant deaths) occurred with TAF- compared to TDF-containing regimens *(45)*. No increase in occurrence of congenital defects or specific pattern of congenital abnormalities has been observed with either drug compared to rates in the general population *(53)*.

The certainty of evidence for boosted or mixed TAF and TDF regimens was rated as moderate for viral suppression and low-to-moderate for safety outcomes. For unboosted TAF and TDF regimens, the certainty of evidence was rated as high for viral suppression and moderate for most safety outcomes. Overall, the certainty of evidence was judged to be moderate.

The systematic review did not identify comparative studies of TDF and TAF in children, as TDF is not recommended for use in younger age groups *(54)*. If treated with TDF-containing regimens, younger prepubertal or early pubertal children (ages when there is rapid skeletal growth) may be at higher risk of decreased bone mineral density with TDF than older children and adolescents with more advanced pubertal development. However, TAF can be used in children due to its lower bone toxicity, and there is in fact growing evidence of its use in children and adolescents. Evidence from studies conducted in children aged over two years and in adolescents has demonstrated good efficacy and tolerability of TAF-containing regimens *(55,56)*. A recent observational study of TAF in children and adolescents in Europe found high viral suppression rates (86% (168/196) at 96 weeks) and good safety and tolerability associated with TAF-based ART *(56)*.

Due to the absence of comparative data for TAF and TDF in children, the certainty of evidence was rated as very low.

3.2.4 Rationale for the recommendation

Balance of effects

The Guideline Development Group considered that the overall balance of benefits to harms favours maintaining tenofovir in the NRTI backbone of subsequent ARV regimens in adults and adolescents, based on efficacy (higher viral suppression and CD4 cell count increase) and safety (lower risk of grade 3 and 4 adverse events and DTG resistance). The group also recognized that tenofovir is already recommended for initial ART due to its proven efficacy and safety profile, and this recommendation consolidates its current endorsement for both initial and subsequent ART.

Among children, the benefits of maintaining ABC in the NRTI backbone of subsequent regimens were also preferred on the basis of a decreased risk of virological failure and DTG resistance, and noncomparative evidence supporting safety. The overall severity and long experience with AZT toxicity were also considered in the judgement.

When comparing the use of TDF and TAF in adults and adolescents with HIV, the Guideline Development Group concluded that benefits and harms were closely balanced. The effects on efficacy (viral suppression) and some safety outcomes (grade 3 and 4 adverse events, severe adverse events, discontinuation due to adverse events and risk of bone fractures) were considered to be similar. Despite low occurrence, TAF-containing regimens showed a lower risk of renal adverse events compared to TDF-containing regimens in some subpopulations. Although TAF has been shown to have positive effects on bone density laboratory markers compared to TDF, the studies were not designed to address fracture risk and were underpowered for this outcome. TAF was also associated with higher rates of dyslipidaemia and weight gain; these differences were small, with unclear clinical impact. In children, where TDF use is not recommended, the Guideline Development Group considered that the overall safety and efficacy profiles of TAF support its use as an alternative to ABC.

Values and preferences

A values and preferences survey conducted for this guideline confirmed that people living with HIV prefer antiretroviral regimens that are effective even with partial drug resistance. They also prefer once-daily fixed-dose combinations with minimal side-effects and little interference with diet or other medications. Antiretroviral regimens that can also treat hepatitis B if the individual has both HIV and hepatitis B are also preferred. They value avoiding side-effects like skin rash, jaundice, gastrointestinal effects, body weight changes and long-term negative effects on bone, renal and cardiometabolic health.

Overall, the Guideline Development Group considered that maintaining tenofovir (in adults and adolescents) or ABC (in children) as part of the NRTI backbone of subsequent ARV regimens is associated with increased benefits and fewer harms when compared to switching to AZT. Decisions may therefore not be sensitive to preferences regarding how patients value different benefits or harms. Regarding the preferential use of TDF or TAF, overall benefits and harms appear to be similar and decisions regarding the use of one over the other therefore do not appear to be preference-sensitive in most situations. However, some patients may place greater importance on avoiding renal adverse events (associated with TDF), or drug interactions and cardiometabolic effects (associated with TAF), and this may impact decisions in some subpopulations or clinical situations.

Cost and cost-effectiveness

In adults and adolescents, recycling TDF in subsequent ARV regimens instead of switching to AZT simplifies treatment protocols and reduces costs. The median prices of TDF-containing regimens are significantly lower than AZT-containing regimens in LMICs. In children, the cost of ABC and AZT are more comparable but vary according to formulation, dosing and setting *(57)*. No studies evaluating the cost-effectiveness of recycling tenofovir or ABC in subsequent regimens were identified.

The median price of TAF is currently 11–54% higher than TDF in LMICs *(58)* but, as TAF requires a lower daily dose to achieve the same effects as TDF, it has a high potential to be much more affordable if procurement volumes substantially increase and generic producer competition is promoted. No cost-effectiveness studies evaluating the use of TAF and TDF in LMICs were identified.

Acceptability and equity impact

The overall acceptability of recycling tenofovir (in adults and adolescents) and ABC (in children) in subsequent ARV regimens is well supported by people living with HIV and health care providers based on high virological suppression rates, reduced harms (including drug resistance risk), maintenance of simplified treatment regimens, low pill burden and easy scalability in treatment programmes. People living with HIV who have tolerated tenofovir or ABC well in their initial regimen are often willing to continue its use. Recycling tenofovir and ABC may also increase equity due to widespread access and relatively low costs compared to other NRTIs, making treatment more affordable for national programmes and people living with HIV.

Pilot projects have shown that TAF is acceptable and feasible for use in LMICs, particularly for specific populations (e.g. persons with renal or bone disease who cannot use TDF) *(59)*. TAF use has the potential to improve health outcomes by providing an additional ART option in populations facing challenges with TDF, thereby improving equity. However, without addressing potential cost and logistic barriers, it could exacerbate health inequities, particularly for rural low-income and marginalized populations.

Feasibility

The Guideline Development Group felt that recycling tenofovir or ABC in subsequent ARV regimens is feasible and can be successfully integrated into HIV treatment programmes. Both drugs have clinical, operational and economic advantages over AZT, providing less toxic, more convenient and simpler treatment protocols, reducing the need for complex drug substitutions and additional laboratory monitoring, and thereby reducing overall treatment costs.

The availability and cost of TDF- and TAF-containing regimens may vary depending on setting and access to generic formulations. TDF is widely available and affordable and has been generally used as the preferred tenofovir prodrug option in the large majority of LMICs. TAF has been used as a safer alternative in some populations and clinical situations, particularly for people with previous renal disease and osteoporosis *(60)*. TAF is registered in many countries, with several suppliers manufacturing generic co-formulations and having full capacity to cover increased demand if needed *(61)*.

Conclusions

The Guideline Development Group now recommends using TDF or TAF in the NRTI backbone in subsequent ARV regimens in adults, adolescents and older children (over 30 kg). This is based on overall moderate certainty of evidence showing improved benefits and reduced harms compared to AZT-containing NRTI backbones, potential cost savings, high acceptability due to treatment simplification and positive equity impact. The recommendation on NRTI recycling aligns with the existing WHO recommendation on the preferred initial NRTI backbone.

For children under 30 kg, the Guideline Development Group recommends considering the use of ABC or TAF in the NRTI backbone for subsequent antiretroviral regimens. This recommendation is based on overall low certainty of evidence suggesting enhanced benefits and reduced harms compared to AZT, simplified treatment leading to good acceptability and the limited availability of TAF formulations for younger children.

In comparing TDF and TAF for adults and adolescents, the Guideline Development Group determined that there is moderate certainty of evidence that both options are similarly balanced in terms of overall benefits and harms, good acceptability and a low-to-moderate comparative cost difference. Choice should be based on patient clinical profile, potential pharmacological interactions with other drugs and programmatic availability.

Tables 3.2 and **3.3** summarize the preferred and alternative initial and subsequent ARV regimens for adults, adolescents and children. **Table 3.4** compares key clinical and programmatic parameters for choosing TDF or TAF.

3.2.5 Implementation considerations

Recycling tenofovir or abacavir in subsequent antiretroviral regimens may affect the demand for these NRTIs. Procurement and supply chain processes should be adjusted accordingly by anticipating an increased need for tenofovir and abacavir while decreasing the need for AZT formulations. Effective monitoring and management of adherence issues are required to sustain the population health benefits of this strategy.

TAF-containing regimens have been used as alternative options for specific situations where TDF should not be used and represent up to 10–20% of procurement demand for tenofovir-containing formulations in a majority of HIV treatment programmes in LMICs that have incorporated them in their drug portfolio *(62)*. Some countries have recently adopted TAF as the preferred tenofovir prodrug option and procurement demand is expected to increase *(63)*. A large and unplanned switch from TDF to TAF regimens as a preferred option may introduce important programmatic challenges in some settings such as increasing drug costs and supply chain demands (e.g. different strength formulations for boosted and unboosted regimens), without significant clinical benefits outside the specific situations where their use is currently recommended. Weighing the benefits and risks of these two options and setting the right procurement plan for both TDF and TAF should be based on a clear clinical and public health rationale.

In individuals with pre-existing mild-to-moderate chronic renal disease, use of TAF may be a preferred option to reduce the impact of tenofovir on renal function. Patients with a clinical history of osteoporosis, chronic use of corticosteroids or medications that may worsen bone density, or a history of fragility fractures may benefit from the use of TAF over TDF.

Rifamycins (including rifampicin, rifabutin and rifapentine) and certain anticonvulsants (such as carbamazepine, phenytoin and phenobarbital) are strong inducers of cytochrome P450 3A4 enzyme and P-glycoproteins, which can significantly lower plasma levels of TAF. However, pharmacokinetic studies have demonstrated that intracellular levels of tenofovir diphosphate are four to five times higher than those achieved with the standard dose of TDF when concomitantly used with rifampicin *(64,65)*. This suggests that the use of TAF 25 mg once daily with rifampicin may be acceptable. There is no significant drug interaction between TDF and rifampicin *(66)*.

In older populations, where renal, bone and cardiovascular comorbidities are common, a balanced risk assessment is recommended for a more appropriate choice between both drug options.

Ritonavir and other pharmacological boosting agents (e.g. cobicistat) may increase plasma levels of tenofovir, which can lead to a higher risk of renal and bone adverse events *(67)*. TAF should therefore be reduced to a 10 mg dose *(68)*. However, a dose-adjusted version of TDF is not available in current formulations: compared to dose-adjusted TAF this has led to an increased risk of treatment discontinuation due to renal events when TDF has been used together with boosting agents *(69)*. The risk of bone and renal adverse events is not significantly different between TDF and TAF when used without booster drugs.

3.2.6 Research gaps

Several research gaps were identified by the Guideline Development Group.

Recycling NRTI backbones in subsequent ARV regimens. Further research is needed to evaluate the durability of virological suppression when recycling TDF, TAF or ABC in treatment-experienced individuals. Attention should be given to the potential emergence of DTG resistance, especially with prior drug exposure and suboptimal adherence. More data is also required to assess potential toxicities associated with prolonged TAF use including weight gain, dyslipidaemia and increased cardiometabolic risk, particularly in ageing populations.

The safety and efficacy of recycling TDF, TAF or ABC in people living with HIV who have failed PI- or INSTI-based regimens – without previous NNRTI exposure – remain unclear. Studies should investigate cross-resistance risks, treatment-limiting toxicities and optimal sequencing strategies. There is a critical need for data on the safety and tolerability of these drugs in subpopulations such as individuals with advanced HIV disease, pregnant women and children. These groups may have unique characteristics that affect drug safety and efficacy.

More investigation is necessary regarding NRTI recycling and drug resistance in those with advanced HIV disease, as current data are insufficient and these patients may be underrepresented in clinical trials, thus limiting their generalizability.

Use of TAF in people living with HIV. It is important to evaluate the cost-effectiveness of TAF-based regimens compared to TDF-based regimens in the LMIC context, including long-term savings from reduced side-effects and complications associated with noncommunicable diseases.

While TAF has been shown to have fewer adverse effects on kidney and bone health according to laboratory markers, additional research is necessary to substantiate these benefits in diverse populations within LMICs, including elderly individuals and those with advanced HIV disease. The prevalence of comorbidities and nutritional status is also likely to vary in these countries. Cardiovascular risk assessment in the context of body weight gain associated with TAF-containing regimens is also needed.

More research is required to determine the safety, efficacy and appropriate dosing of TAF in children, as this population may have different pharmacokinetic profiles and adherence challenges. Comparative studies on TAF versus ABC are necessary. Monitoring the development of drug resistance to TAF in LMICs is important to ensure the long-term efficacy of ART regimens.

Further research should investigate the dosing and efficacy of TAF in people with HIV and TB using rifamycins and other cytochrome P450 (CYP) enzymatic inducers. Studies are also needed to compare TAF-containing triple-drug regimens with simplified dual therapies (e.g. DTG+3TC), particularly in older individuals and those with renal or bone comorbidities. Additional safety data are also required on pregnancy outcomes, breastfeeding, postmenopausal women and the use of TAF-based regimens for preventing vertical transmission of hepatitis B.

Table 3.2 Preferred and alternative initial regimens in adults, adolescents, children and neonates

Populations	Preferred initial regimen	Alternative initial regimen	Special circumstances
Adults and adolescents	TDF (or TAF) + 3TC (or FTC) + DTG	TDF + 3TC + EFV 400mg[a]	TDF (or TAF) + 3TC (or FTC) + EFV 600 mg[a] AZT + 3TC + EFV 600 mg[a] ABC + 3TC + DTG TDF (or TAF[b]) + 3TC (or FTC) + DRV/r (or ATV/r or LPV/r)
Children	ABC + 3TC + DTG	TAF + 3TC (or FTC) + DTG ABC + 3TC + DRV/r[c] (or ATV/r or LPV/r[e])	ABC (or AZT) + 3TC + EFV[d] (or NVP) AZT + 3TC + DRV/r[c] (or ATV/r or LPV/r[e])
Neonates	ABC + 3TC + DTG[g]	AZT + 3TC + NVP	AZT (or ABC) + 3TC + LPV/r[f]

3TC = lamivudine, ABC = abacavir, ATV/r = atazanavir/ritonavir, AZT = zidovudine, DRV/r = darunavir/ritonavir, DTG = dolutegravir, EFV = efavirenz, FTC = emtricitabine, LPV/r = lopinavir/ritonavir, NVP = nevirapine, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate

a. EFV-based ART should not be used in settings where national estimates of pre-treatment resistance to EFV are 10% or higher.

b. In adults and adolescents, TAF daily dosage should be reduced from 25 mg to 10 mg when used with boosted PIs.

c. DRV/r is not approved for children under three years of age.

d. EFV should not be used for children younger than three years of age.

e. ATV/r can replace LPV/r for children over three months old but consider limited formulations for those under six years of age, lack of fixed-dose combination and separate ritonavir booster administration.

f. LPV/r syrup or granules can be used if starting after 2 weeks of age.

g. Dolutegravir (DTG) dose of 5 mg every other day (every 48 hours) in the first 2 weeks of life is safe and maintains appropriate drug levels. At age 2 weeks, DTG dosing is increased to 5 mg once every day.

Table 3.3 Preferred and alternative subsequent ART regimens for adults, adolescents, children and infants

Population	Failing initial regimen	Preferred subsequent regimen	Alternative subsequent
Adults, adolescents and children > 30 kg	TDF (or TAF) + 3TC (or FTC) + DTG	TDF (or TAF[a]) + 3TC (or FTC) + DRV/r	TDF (or TAF[a]) + 3TC (or FTC) + ATV/r (or LPV/r)
	TDF (or TAF) + 3TC (or FTC) + EFV	TDF (or TAF) + 3TC (or FTC) + DTG	TDF (or TAF[a]) + 3TC (or FTC) + DRV/r (or ATV/r or LPV/r) AZT (or ABC) + 3TC + DRV/r (or ATV/r or LPV/r)
	AZT + 3TC + EFV	TDF (or TAF) + 3TC (or FTC) + DTG	TDF (or TAF[a]) + 3TC (or FTC) + DRV/r (or ATV/r or LPV/r) ABC + 3TC + DRV/r (or ATV/r or LPV/r)
	ABC + 3TC + DTG	ABC (or TAF) + 3TC (or FTC) + DRV/r	TAF (or ABC) + 3TC (or FTC) + ATV/r[b] (or LPV/r) AZT + 3TC + ATV/r[b] (or LPV/r)
Children < 30 kg and infants	ABC (or AZT) + 3TC + LPV/r	ABC (or TAF) + 3TC (or FTC) + DTG	ABC (or AZT) + 3TC + DRV/r[c]
	AZT + 3TC + NVP	ABC (or TAF) + 3TC (or FTC) + DTG	ABC (or TAF) + 3TC + DRV/r[c] (or ATV/r[b] or LPV/r)

3TC = lamivudine, ABC = abacavir, ATV/r = atazanavir/ritonavir, AZT = zidovudine, DRV/r = darunavir/ritonavir, DTG = dolutegravir, EFV = efavirenz, FTC = emtricitabine, LPV/r = lopinavir/ritonavir, NVP = nevirapine, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate

a. In adults and adolescents, TAF daily dosage should be reduced from 25 mg to 10 mg when used with boosted PIs.

b. ATV/r can replace LPV/r for children over three months old but consider limited formulations for those under six years of age, lack of fixed-dose combination and separate ritonavir booster administration.

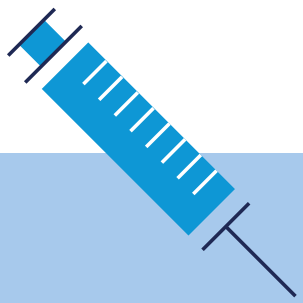
c. DRV/r is not approved for children under three years of age.

Table 3.4 Comparison of tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF)

Major parameters	Favours TAF	Favours TDF	Comments
Renal safety	✓		TAF shows less impact on renal and bone density mineral laboratory markers compared to TDF. Nevertheless, there is a low occurrence and nonsignificant difference in the incidence of clinical events when using TDF or TAF with unboosted regimens. There is a higher discontinuation rate due to renal events when using TDF with boosted PI regimens.
Bone safety	✓		
Dyslipidaemia		✓	TAF associated with a small increase in levels of LDL cholesterol and triglycerides
Body weight gain		✓	TAF associated with a small increase in body weight, particularly when used with INSTIs.
Use with boosted PIs	✓		TAF dose reduction is needed. Lower dose formulations of TDF are not available.
Use in people living with HIV with TB		✓	TAF has important drug interactions with rifamycins, but tenofovir diphosphate maintains therapeutic levels intracellularly.
Use in children	✓		TDF is not recommended for use in young children. TAF dosing for young children not established.
Accessibility in LMICs		✓	Both are available as generic FDCs, but TDF-containing FDCs are largely available and at lower cost than TAF-containing FDCs*.

FDC = fixed-dose combination, INSTI = integrase strand transfer inhibitor, LDL = low density lipoprotein, LMICs = low- and middle-income countries, PI = protease inhibitor, TAF = tenofovir alafenamide, TB = tuberculosis, TDF = tenofovir disoproxil fumarate, TLD= tenofovir+ lamivudine+ dolutegravir

*TAF has a high potential for price reduction if used at higher volumes, but will have a relatively minor impact on the total cost of the regimen as the current price of TLD is already very low and has been driven mainly by other drug components and very high volumes of TLD procurement.



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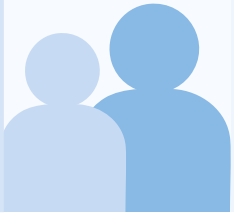
3.3 Use of oral two-drug antiretroviral regimens in HIV treatment

3.3.1 Recommendations



Recommendation 2025

Dolutegravir + lamivudine (DTG+3TC) can be used for treatment simplification in adults and adolescents, with undetectable HIV viral load on 3-drug ARV regimens and without active hepatitis B infection.
conditional recommendation, moderate certainty of evidence

3.3.2 Background

Since the mid-1990s, the use of three active antiretrovirals from at least two different drug classes has been the standard of care for HIV therapy of people living with HIV *(1)*. However, significant advancements in the efficacy and safety profiles of antiretrovirals have been made in recent years. Given that all drugs are associated with potential adverse effects, minimizing the number of drugs used where appropriate (i.e. without reducing efficacy) may be beneficial. The interest in reducing the number of drugs in treatment regimens has grown with the understanding that some antiretrovirals can contribute to age-related end-organ and metabolic comorbidities, an important consideration given the increasing population of people living with HIV over 50 years of age *(2)*.

Several national and regional guidelines now recommend the use of oral two-drug antiretroviral regimens (2DR) as a switching strategy for those virologically suppressed on ART or as an initial treatment in certain circumstances *(3–5)*. The potential benefits of the 2DR approach include reduced lifetime drug exposure, smaller pill size, improved tolerability, lower risk of drug interactions and specific toxicities, and cost savings. These benefits must be balanced against concerns including increased risk of drug resistance, potential impact on coinfection management (e.g. hepatitis B), and limited clinical and programmatic experience in LMICs.

Recent ART switching studies comparing 2DR regimens to standard oral three-drug antiretroviral regimens (3DR) in LMICs have demonstrated comparable virological efficacy, even among people living with HIV with advanced HIV disease *(6)*. With longer life expectancy and rising prevalence of noncommunicable diseases among people living with HIV, which can lead to polypharmacy and increased risk of drug interactions, 2DR can offer clinical and programmatic advantages, particularly for certain populations.

3.3.3 Supporting evidence

Use of oral two drug regimens as a simplification strategy in adults and adolescents with HIV

A systematic review and meta-analysis compared the efficacy and safety of 2DR versus 3DR as ART for people living with HIV. Fourteen studies assessed data for three different 2DR: dolutegravir + lamivudine (DTG+3TC), dolutegravir + rilpivirine (DTG+RPV), and dolutegravir + darunavir/ritonavir (DTG+DRV/r) *(6–18)*.

No significant difference in overall efficacy (HIV RNA < 50 copies/mL) between 2DR and 3DR was found (RR=1.00; 95% CI: 0.99 to 1.02; risk difference 0.00; 95% CI: -0.01 to 0.02). Similarly, no significant difference was observed in viral suppression rates when comparing the 2DR subgroups of DTG+3TC (P=0.74), DTG+RPV (P=0.90) and DTG+DRV/r (P=0.60). No significant difference in overall mortality or within the 2DR subgroups was observed.

Regarding safety outcomes, more statistically significant discontinuations due to adverse events were observed in the 2DR arms compared to 3DR arms overall (RR=1.88; 95% CI: 1.09–3.25). However, in stratified analysis, there was no significant difference between DTG+3TC vs 3DR (P=0.28). The DTG+RPV group had significantly more discontinuations with 2DR than 3DR (3.3% vs 0.6%; RR=5.64, 95% CI: 1.66–19.14). Similarly, the DTG+DRV/r subgroup also showed higher discontinuation rates with 2DR compared to 3DR (10.5% vs 3.8%; RR=2.80; 95% CI: 1.04–7.55; P=0.04). It is important to note that most studies evaluated were switching trials from stable 3DR to 2DR: these often favour the original 3DR already been tolerated by patients.

Regarding total adverse events, no significant difference between trial arms was demonstrated overall (P=0.35). However, a stratified analysis identified a statistically significant increase in the risk of total adverse events with DTG+RPV compared to 3DR. Regarding severe adverse events, no statistically significant difference was identified overall (P=0.83), and no significant differences were observed for any specific 2DR in subgroup analysis.

Treatment-emergent HIV drug resistance was rarely observed. However, the studies reviewed in this meta-analysis included only people without prior HIV drug resistance or history of virological failure.

For DTG+3TC and DTG+DRV/r compared to 3DR, the overall certainty of evidence was assessed as moderate (high for viral suppression and total adverse events, low-to-moderate for mortality, severe adverse events and discontinuation due to adverse events). For DTG+RPV compared to 3DR, the overall certainty of evidence was assessed as low (low for viral suppression and low-to-very low for other outcomes).

People with hepatitis B coinfection were excluded from the analysed studies because the current 2DR regimens in clinical use do not contain tenofovir.

The proportion of participants aged > 50 years old was documented in six trials (10–29% of participants). Pooled age-stratified data showed comparable rates of viral suppression, total adverse events and discontinuation due to adverse events in individuals over 50 compared to those under 50 years old *(15)*.

Use of oral two drug regimens as a simplification strategy in pregnant and breastfeeding women with HIV

None of the studies in the systematic reviews included pregnant women, and direct data on 2DR in pregnant and breastfeeding women with HIV are limited *(19,20)*. However, the efficacy of ARV drugs in pregnant adult populations can be extrapolated from efficacy data from nonpregnant adults, provided that pharmacokinetic data shows similar drug exposure in both groups and safety studies support their use in pregnancy.

Supporting data are available on the pharmacokinetics, safety and efficacy of DTG in pregnant women. The pharmacokinetics of 3TC in pregnancy also indicate systemic exposure consistent with nonpregnancy therapeutic levels, with no dose modification needed in pregnancy *(21–25)*. The safety of individual drugs, including sufficient data to assess rare outcomes such as organ-specific birth defects, as well as their efficacy have been demonstrated in two clinical trials of 3DR containing DTG and 3TC during pregnancy as well as in multiple observational studies in pregnant persons *(26–31)*. There are therefore sufficient data to recommend DTG+3TC in pregnant and breastfeeding women under the same indications as for nonpregnant women.

Evidence suggests that DRV/r is safe and effective for pregnant and breastfeeding women, but the dosing schedule (i.e. once or twice daily, particularly in the last trimester of pregnancy) remains unclear (see Section 3.1.4). Data on the safety and efficacy of DRV/r in pregnancy, in combination with data on DTG in pregnancy as described above, could support the use of DTG+DRV/r as a 2DR in pregnancy. However, gaining a better understanding of the appropriate dosing schedule or DRV/r is an important area for further research.

Existing studies on oral RPV use during pregnancy are very limited, with only 156 reported exposures, and there are no direct studies on DTG+RPV in pregnancy *(32–36)*. Pharmacokinetic data on oral RPV shows significantly lower levels during pregnancy, raising concerns about potential effects on virological efficacy. Pharmacokinetic studies indicate 23–45% lower RPV levels in later pregnancy compared to the postpartum, but viral suppression was largely maintained with no adverse outcomes reported in the small number of women in these studies *(37)*. The Antiretroviral Pregnancy Registry shows a birth defect rate of 2.0% for first trimester RPV exposures, which is comparable to the defect rate observed in population-based registries *(29)*. More pharmacokinetic and efficacy data in pregnancy for 2DR, including oral RPV, is needed.

3.3.4 Rationale for the recommendation

Balance of effects

The Guideline Development Group concluded that, overall, use of a 2DR with DTG has effects that are similar to a 3DR, with potential benefits for specific individuals or clinical situations, e.g. persons with renal or bone disease who cannot use TDF (none of the 2DR DTG regimens evaluated include TDF). Efficacy (viral suppression, mortality) and certain safety outcomes (total adverse events, severe adverse events) appear similar for 2DR and 3DR. Although 2DR were associated with an increased risk of discontinuation due to adverse events versus 3DR, this finding was driven by an increased risk associated with DTG+RPV and DTG+DRV/r which was not observed with the DTG+3TC subgroup. In addition, this finding was based on trials switching from stable 3DR to 2DR, which is likely to bias results against the 2DR, since these patients have already demonstrated that they tolerate the 3DR. Overall, the evidence on the safety and efficacy of 2DR, particularly for DTG+3TC, is consistent among adults and adolescents, but there are some limitations and research gaps for DTG+RPV (potential subtherapeutic levels) and DTG+DRV/r (ideal dosing schedule) in pregnant women. DRV/r and RPV cannot be used in people with HIV-associated TB due to important drug interactions with rifampicin. None of these 2DRs is suitable for people living with HIV with active hepatitis B coinfection as they do not include tenofovir, and a pre-treatment screening or history of previous immunization may be necessary prior to initiation of 2DR

Values and preferences

A values and preferences survey conducted for this guideline confirmed that people living with HIV prefer antiretroviral regimens that are effective even with partial drug resistance. They also prefer once-daily fixed-dose combinations with minimal side-effects and little interference with diet or other medications. In persons with both HIV and hepatitis B, antiretroviral regimens that can also treat hepatitis B are preferred. People living with HIV noted that they value avoiding side-effects like skin rash, jaundice, gastrointestinal symptoms, body weight changes and long-term negative effects on bone, renal and cardiometabolic health (Web Annex C).

The Guideline Development Group considered that overall benefits and harms appear to be similar between 2DR and 3DR and decisions would therefore not be preference-sensitive in most situations. However, some patients may place greater importance on avoiding adverse events, which are more likely to be associated with switching to DTG+RPV and DTG+DRV/r combinations. The need to screen for other infections (hepatitis B, TB) or an increased risk of HIV drug resistance may also influence decisions on the use of 2DR.

Cost and cost-effectiveness

Most single ARVs formulations used in 2DR options are largely available in LMICs but registration of these regimens as fixed-dose combinations is still limited. Only DTG+3TC as a generic FDC is available and used in a few LMICs. While DTG+3TC costs are similar to or slightly cheaper than TLD, other 2DR options like DTG+DRV/r and DTG+RPV are more expensive, even in generic formulations *(38)*.

With increased use and generic competition, the prices of 2DR options are expected to decrease. However, some upper middle-income countries face patent and licensing restrictions preventing access to cheaper generic DTG, DRV/r and RPV. Availability of generic oral RPV formulations in LMICs is very limited *(39)*.

Studies in high-income settings show DTG+3TC as a 2DR is cost-effective and -saving compared to 3DR options for treatment-naive and switching options although nongeneric formulations were used in the analysis *(40)*. A Spanish study found that nongeneric DTG+RPV was cost-saving for treatment-experienced patients *(41)*. No cost-effectiveness studies in LMICs were identified.

Acceptability and equity impact

The overall acceptability of 2DR as a simplification strategy is well supported by people living with HIV and health care providers owing to its good safety and tolerability profile and high efficacy in all populations when compared to 3DR options. Other factors include its availability as a once-daily co-formulation and good comparative cost. ART simplification using 2DR appears to be a viable option, offering clinical and programmatic benefits for managing certain subpopulations. Generally, the overall tolerability of an ART regimen is of greater concern for people living with HIV rather than the number of drugs in the regimen. The HIV Treatment Satisfaction Questionnaire Score (HIVTSQ) collected in some trials (SALSA, SWORD) showed comparable or higher scores for 2DR versus 3DR *(39,40)*. In a qualitative study investigating medication beliefs among people living with HIV in Zimbabwe, individuals preferred fewer daily pills and ART that minimizes side-effects and drug interactions. However, the number of drugs in a regimen was not mentioned as a concern *(41,42)*. For adolescents, a survey conducted for this guideline review evaluated 192 adolescents and young people from 15 countries regarding 2DR. The survey found that 43% of participants expressed their willingness to use dual therapy (Web Annex C).

Use of 2DR has the potential to improve health equity, particularly in some subpopulations that can face challenges with use of TDF or TAF in the presence of chronic renal, bone and/or cardiovascular comorbidities (particularly in elderly populations). Hepatitis B coinfection is a concern in low- and middle-income settings: without addressing potential cost and logistic needs associated with the implementation of hepatitis B screening, 2DR could potentially exacerbate health inequities, particularly among rural, low-income and marginalized populations. Access to generic 2DR FDCs can be limited in some countries due to patent barriers.

Feasibility

Adopting 2DR, especially DTG+3TC, as a treatment simplification strategy is feasible and has been rolled out in several LMICs. Brazil has implemented DTG+3TC for people living with HIV on ART, particularly those aged 40–50 years with renal and/or bone disease or at high cardiovascular risk *(3)*. Botswana uses DTG+3TC for patients stable on first-line ART with CD4 count > 200 cells/mm^3 and no hepatitis B coinfection *(4)*.

Many countries have not yet included 2DR in their guidelines and procurement protocols, but several suppliers are manufacturing generic 2DR single and dual formulations with the capacity to cover increased demand, though this is more limited with RPV oral formulations.

Conclusions

The Guideline Development Group conditionally recommends DTG+3TC for simplifying ART in adults and adolescents on 3DR with undetectable HIV viral load and without active hepatitis B coinfection. This judgement was based on moderate certainty of evidence showing similar benefits and harm effects compared to 3DR, potential advantages for specific subpopulations that have to avoid using tenofovir, similar costs, good acceptability and potential positive equity impact. The limited availability of generic dual FDCs and lack of cost-effectiveness studies in LMICs were noted.

3.3.5 Implementation considerations

2DR has been adopted as a simplification strategy in many clinical guidelines for people living with HIV with chronic renal, bone and/or cardiometabolic conditions where use of tenofovir should be avoided. This has particularly been the case for elderly populations affected by multiple chronic comorbidities and at risk of drug interactions due to polypharmacy *(43)*. Hepatitis B serological status must be determined as a key eligibility criterion, and if active hepatitis B/HIV coinfection is present, a hepatitis B-active drug should be added. The use of point-of-care technologies and integration with other screening policies are recommended to facilitate implementation *(44)*.

Overall, people living with HIV who are on 3DR, have undetectable viral load and no active hepatitis B coinfection are eligible for 2DR simplification. The use of 2DR as initial therapy may also be considered and is supported by recent clinical trials, even in those with more advanced disease and without previous drug resistance screening *(6,15,16)*. However, experience in LMICs is limited and close clinical and viral load monitoring advised.

DTG+3TC is recommended as the preferred 2DR option due to its clinical and programmatic advantages as well as more extensive clinical experience compared to other 2DR options. In addition, unlike other DTG-based 2DR, trials indicated that switching to DTG+3TC is not associated with more withdrawals due to adverse events compared to continuing on a 3DR. DTG+DRV/r and DTG+RPV also have other important limitations, such as drug interactions with rifampicin and other medicines, issues with dosing in pregnant women, higher comparative costs, limited access to generic formulations and less experience in the LMIC context. DTG+3TC can be used in people living with HIV-associated TB following a rifamycin-based treatment for TB disease, but the DTG dose should be adjusted *(45)*. In people with severe renal impairment, the 3TC dose should also be adjusted *(46)*.

3.3.6 Research gaps

Research should focus on the efficacy of 2DR strategies, especially DTG+3TC, in areas with high prevalence of primary NRTI resistance and where programmatic TLD transitions took place without viral load testing. Studies evaluating the frequency of viral load monitoring in PLHIV using 2DR regimens should be conducted. Long-term adherence to 2DR and its impact on the development of DTG resistance are also important. Cost-effectiveness studies comparing DTG+3TC with other 2DRs, and studies on DTG+3TC as initial therapy in LMICs, are necessary. The safety and efficacy of 2DR, particularly DTG+RPV and DTG+DRV/r, should be evaluated in pregnant women. The occurrence of long-term metabolic effects with use of 2DR compared to 3DR also requires assessment. Management strategies for individuals failing on 2DR should also be addressed.

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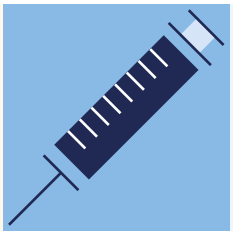
3.4 Use of long-acting injectable antiretroviral regimens in HIV treatment

3.4.1 Recommendations



Recommendation 2025

Long-acting injectable cabotegravir + rilpivirine (CAB+RPV) can be used as an alternative switching option in adults and adolescents who have an undetectable HIV viral load on oral ART and no active hepatitis B infection.
conditional recommendation, moderate certainty of evidence

3.4.2 Background

While current once-daily oral combinations are highly effective and tolerable, people face adherence challenges for a variety of reasons and, increasingly, drift in and out of care. Certain populations, including adolescents, postpartum women and people with high levels of substance use and marginal housing face heightened adherence challenges. Long-acting HIV treatment could enhance adherence and provide coverage during periods of disengagement from care. Long-acting ARV regimens offer benefits such as reduced dosing frequency, convenience and privacy, potentially leading to improved adherence. However, access to long-acting HIV medications remains restricted, particularly in low-income settings and marginalized communities. There are concerns regarding drug resistance, coinfection management, and cost and implementation challenges *(1,2)*.

For adolescents, adherence to treatment and side-effects from ART are crucial issues *(3)*. Providing treatment options to adolescents and young people is essential due to the multifaceted barriers they encounter in maintaining treatment adherence, including forgetfulness, frequency and number of pills, difficulties in swallowing medications and side-effects. Other populations with adherence challenges, such as postpartum women and patients with high levels of substance use and limited resources or other socioeconomic barriers, could also benefit from effective long-acting ARV *(4)*.

Cabotegravir + rilpivirine (CAB+RPV) is the only long-acting injectable ARV regimen approved for HIV treatment and has been adopted by some treatment guidelines as a switching strategy for people living with HIV already on ART and with viral suppression *(5)*. WHO has recently made recommendations for the use of CAB for pre-exposure prophylaxis (PrEP) *(6)* but no recommendations exist concerning the use of long-acting ARVs for HIV treatment.

3.4.2 Supporting evidence

Use of long-acting injectable antiretroviral regimens in adults and adolescents with HIV

A systematic review and meta-analysis examined the efficacy, safety and risk of INSTI resistance with long-acting injectable CAB+RPV *(7)*. All studies assessed switching to long-acting injectable CAB+RPV in people already on ART and virologically suppressed with an undetectable viral load (HIV RNA < 50 copies/mL) as a switching strategy. Six randomized clinical trials directly compared efficacy outcomes (viral suppression and confirmed virological failure). The results indicated no significant differences between long-acting CAB+RPV and standard oral therapy (SOT) for viral suppression (RR= 0.98; 95% CI: 0.90–1.06) or confirmed virological failure (RR=0.93; 95% CI: 0.32–2.70) at 96 weeks.

In terms of safety outcomes, the systematic review assessed the incidence of grade 3 and 4 adverse events, discontinuations due to adverse events and the emergence of INSTI resistance. Meta-analysis found that CAB+RPV was associated with a significantly higher risk of grade 3 and 4 adverse events compared to SOT (RR1.48; 95% CI: 1.15–1.90) and discontinuations due to adverse events (RR=2.61; 95% CI: 1.40–4.88) at 96 weeks. The review also found a higher risk of INSTI resistance in individuals with virological failure (RR=5.50; 95% CI: 1.43–21.8). A complementary meta-analysis of 33 studies (25 cohorts, seven randomized trials and one nested randomized trial) found that virological failure was rare (2%; 95% CI: 1–3%) *(7)*. Consequently, INSTI resistance among all CAB+RPV users was also a rare occurrence.

An additional safety analysis conducted at 48 weeks of follow-up found that the incidence of total adverse events was significantly higher with CAB+RPV treatment compared to SOT (RR=1.22; 95% CI: 1.12–1.33) *(7)*. This risk persisted even when injection site reactions were excluded from the analysis (RR=1.10; 95% CI: 1.03–1.19). CAB+RPV treatment was also associated with more weight gain, increased LDL levels, a smaller increase in CD4 cell count and a higher risk of hypertension compared to SOT. However, the absolute differences were small.

The overall certainty of evidence regarding the desirable and undesirable effects was rated as moderate.

Some complementary cohort data on the use of long-acting injectable CAB+RPV in adolescents living with HIV in the MOCHA study showed that approximately 11% of participants had at least a grade 3 adverse event by week 24. Mild injection site reactions were reported in 30% of participants. However, there was no reported severe adverse event or treatment discontinuation due to adverse events *(8)*. Mild injection site reactions were reported in 30% of participants. However, there was no reported severe adverse event or treatment discontinuation due to adverse events in this study *(9)*.

Use of long-acting injectable antiretroviral regimens in pregnant and breastfeeding women with HIV

There is very limited evidence on the safety and effectiveness of long-acting CAB+RPV treatment during pregnancy and breastfeeding, and no data from LMICs. Pharmacokinetic data on injectable CAB from pre-exposure prophylaxis and a few treatment studies including pregnant women indicate that CAB dosing during pregnancy results in CAB drug levels within the therapeutic range on both monthly and bimonthly dosing *(10)*. As observed with oral dosing, pharmacokinetic data and modelling based on injectable RPV indicate that RPV levels are significantly reduced in pregnancy, although it is unclear if this affects viral efficacy *(11,12)*. Data on pregnancy outcomes for injectable RPV are also limited (see Section 3.3.2).

There are limited data on long-acting CAB pre-exposure prophylaxis (PrEP) during pregnancy: they show that pregnancy-related maternal adverse event incidence and adverse infant outcomes were similar for women receiving oral long-acting CAB and those receiving PrEP, and comparable to estimated general population outcomes *(13)*.

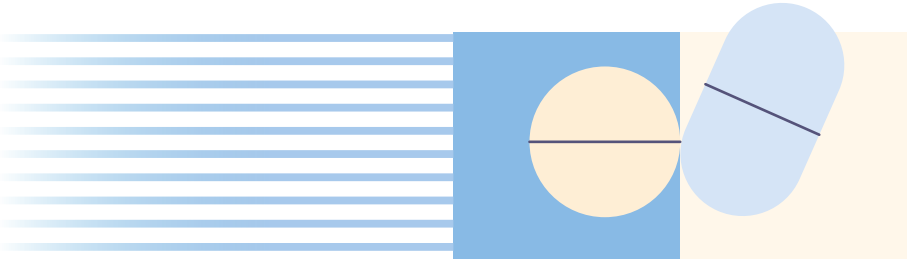
Use of long-acting injectable antiretroviral regimens in children with HIV

There is very limited data on long-acting injectable CAB+RPV for children. A study assessing the use of oral and intramuscular long-acting CAB+RPV in children aged 2–12 years found that by week 12, eight out of 20 children had minor adverse events, mostly injection site reactions. All children maintained virological suppression with drug levels similar to adults *(14)*.

3.4.3 Rationale for the recommendation

Balance of effects

The effects of long-acting injectable CAB+RPV on viral suppression and risk of virological failure are similar to those observed with SOT in patients with an undetectable viral load on ART, although there is an increased risk for some adverse events. In addition, while the incidence of virological failure is low, among those who do experience virological failure long-acting injectable CAB+RPV is associated with an increased risk of INSTI cross-resistance. The Guideline Development Group found important trade-offs between long-acting injectable CAB+RPV versus standard ART, taking the view that the overall benefits of using long-acting injectable CAB+RPV might outweigh the harms in specific clinical situations or populations, e.g. adults and adolescents with an undetectable HIV viral load, but face adherence challenges associated with daily oral ARV regimens and the development of INSTI cross-resistance. The Guideline Development Group considered that the overall benefits of using long-acting injectable CAB+RPV might outweigh the harms in specific clinical situations or populations, such as adults and adolescents with undetectable HIV viral load but face adherence challenges with oral daily ARV regimens. The Guideline Development Group noted concerns including insufficient long-term data on CAB+RPV use in LMICs, limited safety and efficacy data for pregnant women, and the lack of hepatitis B-active drugs in current long-acting regimens, making them unsuitable for those with hepatitis B coinfection. Furthermore, RPV cannot be used in people with TB coinfection who are on rifampicin-containing regimens due to the significant risk of drug interaction.



Values and preferences

A values and preferences survey conducted for this guideline confirmed that people living with HIV are in favour of taking injectable antiretroviral regimens every two months or more, even if separate injections are required for each injectable and complementary oral treatment is needed to treat other conditions. Antiretroviral regimens that can also treat hepatitis B are also preferred by individuals with HIV and hepatitis B coinfection. They also value avoiding side-effects like skin rash, jaundice, gastrointestinal symptoms, body weight changes and long-term negative effects on bone, renal and cardiometabolic health.

The Guideline Development Group determined that for most patients, the decision to use long-acting injectable CAB+RPV is likely to be preference-sensitive. They found no important uncertainty in how patients valued the main outcomes but acknowledged that the importance of benefits and harms could vary in specific situations. Some patients, given the similar virological efficacy of CAB+RPV and standard oral ART, might be motivated to accept the challenge of adhering to lifetime daily oral treatment or, on the other hand, be less concerned about pain and other site reactions associated with deep intramuscular injections, factors which could influence their decisions about the use of injectable long-acting ARVs.

Cost and cost-effectiveness

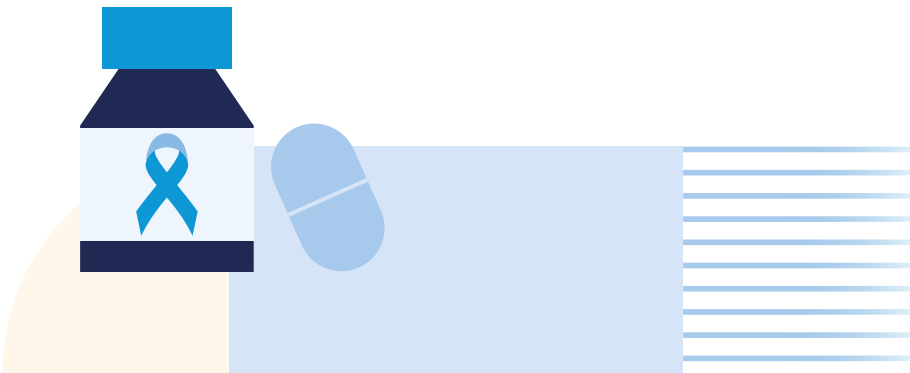
Approximately 15 000 patients globally are using CAB+RPV in real-world cohorts, almost all of them in high-income countries *(15)*. Less than 5% of people living with HIV are in countries where CAB+RPV is commercially available. Among high-income countries, the current price of CAB+RPV formulations ranges between US$8500 to US$10 000 per patient per year (PPY) in Europe, and approximately US$25 000 PPY in the United States *(16,17)*. An affordable price for a long-acting CAB+RPV regimen in HIV treatment for LMICs has not been established.

A modelling analysis study suggests that the estimated costs for generic long-acting CAB for pre-exposure prophylaxis could range between US$30–40 PPY at launch and US$14–18 PPY at medium-scale volumes *(18)*. Lower-cost generic versions of long-acting CAB for prevention are being developed by some generic companies as part of a voluntary licensing agreement, but it is still not clear when large volumes of the generic versions will become available and at what price *(19)*. There is no information available on the potential generic costs of RPV LAIs.

Several cost-effectiveness studies in high-income countries support the use of CAB+RPV as a simplification strategy in virally suppressed individuals. These studies have demonstrated that CAB+RPV was associated with better cost-effectiveness and -utility parameters, being cost-saving in some situations, when compared to daily oral ART *(20–22)*. A modelling study utilizing pooled analysis from CAB+RPV phase 3 trials and adopting the Canadian health service perspective indicated that, compared to oral daily therapy, CAB+RPV could result in cost savings (US$1.5 million per 1000 treated patients), health benefits (107 QALYs and 138 life years), and reduced transmission (three new cases averted per 1000 patients treated) *(23)*.

In LMICs, there are a few modelling studies supporting the use of CAB+RPV as a simplification strategy in populations with adherence challenges, provided formulations are available at significantly reduced prices. A cost-effectiveness study analysed the potential role of CAB+RPV for HIV treatment in sub-Saharan Africa. Assuming a CAB+RPV cost of US$120 PPY, it was found to be borderline cost-effective (median cost per DALY averted across setting scenarios was US$404) if targeted at people living with HIV with suboptimal adherence to ART *(24)*.

Another cost-modelling study considered the cost-effectiveness of introducing CAB+RPV treatment for adolescents in Kenya and found it could be cost-effective compared to daily oral ARV therapy if the cost of CAB+RPV was less than double the current cost of administering oral ART (i.e. an additional annual cost of US$89 or less). Further prioritizing administration to adolescents and young adults who have difficulty taking daily pills but can more easily adhere to long-acting ART could enhance cost-effectiveness *(25)*.



Another modelling study examined the cost-effectiveness of introducing CAB+RPV treatment for breastfeeding women in Zimbabwe compared to the standard care of continuing TLD in women with and without viral suppression at delivery. This study concluded that switching to CAB+RPV at delivery for the subgroup of breastfeeding women with a history of adherence challenges on TLD (i.e. non-suppressed at delivery) could reduce infant infections and save costs. Switching to CAB+RPV at delivery for the substantial number of breastfeeding women with viral suppression on TLD could improve outcomes and be cost-effective only if the cost remained less than US$84 annually *(26)*.

Overall, these cost-effectiveness studies support the use of CAB+RPV as a switching strategy, suggesting that despite the initial higher cost of CAB+RPV compared to oral ARV regimens, there are potential long-term cost savings and health benefits, particularly in high-income settings. In LMICs, where CAB+RPV formulations are currently not readily available, modelling studies suggest that it could be cost-effective for populations with adherence challenges, assuming lower-cost generic formulations become available and are accessible.

Acceptability and equity impact

The overall acceptability of long-acting injectable CAB+RPV is high, especially in scenarios where adherence to oral daily ARV regimens presents a challenge. In high-income settings, several acceptability studies have confirmed a strong preference among patients for long-acting ARVs in implementation and real-world efficacy trials *(8,27)*. Healthcare providers also expressed positive views regarding the sustainability of implementing long-acting injectable ARVs, noting the need for adjustments in clinical protocols and the strengthening of health services *(27,28)*.

In LMICs, there are few acceptability studies due to current limited use in these contexts; however, available research also indicates good acceptance *(29)*. A qualitative study conducted in Uganda reported excellent acceptability and improved adherence compared to daily oral regimens, highlighting reduced psychological burden, enhanced privacy and decreased stigma *(30)*. A qualitative analysis of a recent implementation trial conducted among adolescents and young adults aged 12–24 years in South Africa (AFINAty study) demonstrated high acceptability of long-acting injectable CAB+RPV with high retention and appropriate timing of injections *(31)*.

The use of long-acting injectable ARVs holds the potential to enhance health equity, particularly for specific subpopulations, including adolescents and young adults facing clinical or social challenges with adherence to daily oral regimens. Nevertheless, it is imperative to address the costs and logistics associated with implementing HIV and TB screening and service infrastructure needed to administer long-acting injectable CAB+RPV. Failure to do so may exacerbate existing health inequities, especially for rural, low-income and marginalized populations. It is also important to assess and support adherence challenges, as suboptimal adherence may be an indication of an important psychosocial need.

Feasibility

The feasibility of using long-acting injectable ARVs depends on access to available and affordable formulations, health care infrastructure adjustments and adequate training of health providers to provide administration and follow-up. Real-world analyses are necessary to evaluate external factors such as appointment scheduling as numbers increase. Adoption of CAB+RPV in some high-income countries shows promise, especially for virologically suppressed individuals and those with adherence issues. Improving affordability and availability in LMICs is, however, a pressing priority.

Challenges include higher costs compared to oral medications, lack of generic formulations, lack of trained health care providers, health infrastructure, cold chain and storage needs, slow approval by national drug regulatory authorities and limited access. As of end 2024, CAB+RPV was approved in 46 countries, representing 5% of all people living with HIV. Long-acting CAB for HIV PrEP was licensed within the Medicines Patent Pool (MPP) in 2022. Since RPV patents are set to expire in 2027 and the same CAB formulation is used for both PrEP and treatment, expanding the licence to include treatment could enable access to long-acting injectables such as generic CAB+RPV in LMICs *(19)*.

Strategies to overcome barriers include promoting generic production agreements and price negotiations, setting up training programmes for health care workers, investing in health care facilities, expediting regulatory approvals, and developing community engagement and public-private partnerships. Pilot programmes can help identify barriers.

For adolescents, willingness to use new products is high, but they need clear information, counselling and support. Implementing long-acting ART requires considering local contexts, ensuring collaboration between stakeholders, managing co-conditions and comorbidities, and providing accessible information and supportive systems.

Conclusions

The Guideline Development Group conditionally recommends injectable long-acting CAB+RPV as an alternative switching strategy for individuals with undetectable viral load on oral ART and without active hepatitis B coinfection. This is based on moderate certainty of evidence showing overall benefits similar to SOT, but with some increased harm. Subpopulations facing adherence challenges with oral therapies may particularly benefit. Acceptability of long-acting CAB+RPV appears high, and there is potential for this approach to become cost-effective if generic formulations are available, with potential positive impacts on equity. However, use of long-acting CAB+RPV is currently limited in LMICs due to lack of generic formulations, and uncertain estimates of drug prices and implementation costs.

3.4.4 Implementation considerations

Eligibility criteria for the use of long-acting ARV therapies as a switching strategy should be clearly established, which includes identifying and monitoring populations with undetectable HIV viral load but facing persistent adherence challenges with SOT. This needs to be done within a person-centred approach to ensure equity, as the people likely to most benefit from this strategy are paradoxically those who frequently struggle to access health care or receive newer interventions.

It is essential to develop a health care infrastructure able to administer intramuscular injections. This entails ensuring adequate facilities for injections, planned injection schedules, and storage and safe disposal of syringes and medical waste. Furthermore, a cold-chain infrastructure is required for current long-acting RPV formulations. Treatment services must provide training for health care providers on the safe administration of deep intramuscular injections using the “Z technique” *(32)*.

An important consideration is the lack of antiviral activity of current long-acting ARV regimens against hepatitis B, particularly in LMICs. Additionally, RPV exhibits strong interactions with rifampicin, preventing their concomitant use. Consequently, screening protocols for hepatitis B and TB disease should be integrated into eligibility criteria and clinical follow-up.

For people living with HIV on CAB+RPV who develop tuberculosis, HIV treatment must be modified due to the significant drug interactions with rifampicin. Co-administration of rifampicin with these long-acting formulations is likely to result in subtherapeutic concentrations of both drugs *(33)*. Patients should switch to TLD or an alternative oral regimen that does not significantly interact with rifampin until the end of TB treatment. Other rifamycins (rifabutin and rifapentine) also have significant drug interactions with CAB and RPV and should not be used concomitantly *(34)*.

It is important for HIV treatment programmes introducing the use of long-acting ARVs to establish programme protocols to monitor adverse events associated with the administration and use of long-acting injectable ARVs, as well as to assess and manage drug resistance and failure associated with long-acting ARVs.

3.4.5 Research gaps

The Guideline Development Group identified several important research areas to improve the implementation of CAB+RPV and other long-acting ARVs in HIV programmes. These areas include efficacy studies of CAB+RPV for viraemic patients facing adherence challenges, monitoring the development of drug resistance and identifying associated risk factors, as well as conducting pharmacokinetic and safety studies in pregnancy, and pharmacokinetic and efficacy studies in morbidly obese individuals. Documenting innovative approaches for using long-acting ARVs within marginalized populations, including community support initiatives, are also needed. The Guideline Development Group also emphasized the need for studies on viral resuppression using oral regimens such as TLD in cases of treatment failure, cost-effectiveness analyses across various scenarios and improved treatment monitoring strategies.

Setting up further studies on the pharmacokinetics, safety and efficacy of CAB+RPV and other long-acting ARVs for children is crucial to advance paediatric HIV treatment. There is limited data on the effectiveness and safety of RPV during pregnancy and breastfeeding.

Lenacapavir (LEN) and other newer long-acting agents in the HIV drug pipeline have not undergone thorough evaluation in large, randomized trials for long-acting treatment regimens. Although few trials have been conducted that do not involve CAB+RPV, drug combinations like LEN+CAB are attracting increasing interest, particularly due to recent advancements in optimized formulations for CAB that may enable dosing intervals of four to six months *(35)*. Additionally, weekly oral therapies combining several new long-acting ARV agents, including drugs with enhanced resistance profiles, are currently under investigation *(36)*.

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04

Management of vertical HIV transmission

4. Management of vertical HIV transmission

4.1 Infant postnatal prophylaxis

4.1.1 Recommendations

Good practice statement (2016)

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

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

Recommendations (2025)

Infants who are not at high risk of acquiring HIV should receive six weeks of infant prophylaxis with a single drug, with NVP as the preferred option.
strong recommendation, moderate certainty of evidence

DTG or 3TC are alternative options.
conditional recommendation, very low certainty of evidence

Infants who are at high risk of acquiring HIV should receive a three-drug regimen, with ABC/3TC-DTG as the preferred option.
strong recommendation, low certainty of evidence

Breastfeeding infants who complete six weeks of a three-drug regimen should follow with single-drug prophylaxis until maternal viral suppression is achieved or for the remainder of breastfeeding. NVP is the preferred option *[strong recommendation, moderate certainty of evidence]*. **DTG** *[conditional recommendation, very low certainty of evidence]* or **3TC** *[conditional recommendation, moderate certainty of evidence]* are alternative options.

High-risk infants are defined as those:

- born to women with established HIV infection who have received less than four weeks of ART at the time of delivery;

or

- born to women with established HIV infection with viral load >1000 copies/mL in the four weeks before delivery, if viral load is available; or
- born to women with incident HIV infection during pregnancy or breastfeeding;

or

- born to women identified for the first time during the postpartum period, with or without a negative HIV test prenatally.

4.1.2 Background

Despite expanded maternal ART coverage and improved maternal viral suppression rates with newer DTG-based regimens, vertical transmission persists with an increasing proportion of new infant infections now occurring during the postnatal period *(1)*. Initiating infant ARV prophylaxis shortly after birth remains a key strategy to reduce the risk of HIV transmission in the intrapartum or early breastfeeding period. However, normative guidance is also needed on the use of ARVs for infant prophylaxis in the context of an ongoing risk of HIV acquisition throughout the breastfeeding period, particularly if maternal ART continuity is uncertain: this reflects the fact that an elevated maternal viral load is one of the most significant risk factors for infant HIV acquisition *(2,3)*.

Since 2016, WHO has recommended a risk-stratified approach with enhanced prophylaxis for infants at higher risk of acquiring HIV which is based on more than one ARV for the first six weeks of life, extended for up to 12 weeks for breastfeeding infants *(4)*. Infants at high risk of HIV acquisition were determined to be those whose mothers had a VL ≥ 1000 copies/mL (unsuppressed) at least by late pregnancy, at the time of delivery or during breastfeeding.

In the absence of maternal ART in mothers known to have HIV infection or who are newly diagnosed with HIV infection, enhanced infant prophylaxis using more than one ARV and initiated after birth for the first six weeks of life reduces the risk of intrapartum infection in non-breastfed infants *(5)*. However, in high-risk scenarios where maternal viral suppression has not been achieved at the time of delivery, extending infant prophylaxis until 12 weeks is considered an adequate time period to achieve viral suppression following maternal ART initiation. Routine early infant testing results should also be available to establish infant HIV status and begin treatment in infants following in utero, intrapartum or early postpartum HIV infection. In breastfeeding infants the risk of HIV vertical transmission is extremely low in the context of continuous maternal ART.

Since the WHO 2016 guidance was published, there has been a global scale-up of dolutegravir-based regimens, which are effective and safe to use during pregnancy and breastfeeding; accordingly, an increasing proportion of women are entering pregnancy already on ART.

A review of national policies in 18 high-burden countries in the WHO African Region revealed wide differences in the uptake of the 2016 WHO infant postnatal prophylaxis recommendations *(6)*. Some national policies have adopted enhanced and/or extended prophylaxis as a universal approach in order to simplify guidance, particularly in settings with unreliable or low maternal viral load coverage where risk stratification is challenging to implement.

In the context of maternal ART, the expanded use of enhanced prophylaxis regimens to address concerns about maternal viraemia in the postpartum period *(7)* must be balanced against avoiding unnecessary infant exposure to drugs.

Additionally, since the original development of the WHO recommendations in 2016, new options for safely dosing ARVs in the neonatal period have become available *(8)*. This made it necessary to revisit the recommendations on the use of ARVs in HIV-exposed infants in order to reduce the risk of postpartum HIV transmission. Furthermore, TLD scale-up has resulted in an almost complete global phase-out of NNRTI-based regimens for initial treatment of HIV infection across all populations. This 2025 guideline update aims to further optimize subsequent lines of treatment using better NRTI backbones, which includes phasing out suboptimal options such as AZT in favour of less toxic, more affordable and more convenient options.

4.1.3 Supporting evidence

A systematic review of clinical trials of postnatal prophylaxis in infants at risk of perinatally-acquired HIV infection identified 10 randomized control trials that provided both direct and indirect evidence to inform these recommendations *(9–18)*. All trials but one were conducted prior to 2013, when lifelong ART for all pregnant and breastfeeding women was first recommended by WHO as standard of care *(19)*.

Routine postnatal prophylaxis for all HIV exposed infants

Systematic review found no trials comparing enhanced or extended ARV prophylaxis during breastfeeding compared to single-drug prophylaxis when mothers are on ART and virally suppressed. However, another systematic review on the risk of postnatal transmission during breastfeeding provides indirect evidence suggesting that in women who have been on at least four weeks of ART and have a VL < 1000 copies/mL, the risk of overall transmission is < 1% at six weeks *(2)*. Two other studies on maternal ART use provided additional indirect evidence on more effective use of postnatal ARV prophylaxis in the context of maternal ART. In one trial, randomized pregnant women were newly initiated at more than 28 weeks gestation on DTG- or efavirenz (EFV)-based ART and all infants received six weeks of NVP. Excluding three infants in the DTG arm with intrauterine infection, no additional infections occurred in the 103 infants in the DTG arm and only one late postnatal infant infection was identified in the 103 infants in the EFV-based ART arm through 72 weeks of follow-up. In short, six weeks of infant NVP resulted in no infant HIV transmissions intrapartum or during breastfeeding when mothers had received DTG-based ART for four or more weeks prior to delivery and transmission occurred in < 1% when mothers had been on EFV-based ART for four or more weeks prior to delivery *(20,21)*.

A second trial conducted across six countries also randomized pregnant women between 14- and 28-weeks' gestation before initiating one of two DTG-based regimens versus an EFV-based ART regimen. All infants received the standard of care for postnatal prophylaxis based on national guidelines, which varied between countries. One infant with HIV infection was identified at six weeks of age (DTG arm) and one at 50 weeks (EFV arm). As with the findings from a recent trial among mothers on ART for at least four weeks prior to delivery whose infants received six weeks of single-drug infant prophylaxis, only one perinatal HIV infection was identified among 557 infants receiving at least one HIV test at six weeks of age *(22)*.

Enhanced postnatal prophylaxis for infants in the context of maternal viraemia at the time of delivery

Three clinical trials provided evidence on the use of enhanced postnatal prophylaxis to reduce the risk of vertical transmission in the context of either no maternal ART or suboptimal maternal ARV prophylaxis *(10,13,14)*.

One study randomized non-breastfed infants born to women not on ART into the following groups: single ARV prophylaxis using AZT for six weeks, AZT for six weeks with three doses of NVP during the first eight days of life (two-drug group) or AZT/3TC/nelfinavir (NFV) for two weeks followed by AZT alone to complete six weeks of infant prophylaxis (three-drug group). Both dual- and triple-drug infant prophylaxis regimens were superior to AZT alone in reducing intrapartum infection (4.8% vs 2.2% vs 2.4%, respectively) *(13)*.

Another infant prophylaxis strategy was used in a study in which non-breastfed infants of women with HIV who had received less than eight weeks of ART at the time of delivery received triple-drug prophylaxis using AZT+3TC+NVP for two weeks plus AZT+3TC for an additional two weeks: it demonstrated an intrapartum transmission rate of 0.3% using this enhanced infant prophylaxis *(14)*.

The third large trial also evaluated both enhanced and extended postnatal prophylaxis in breastfed infants born to mothers not on ART after early HIV transmission had been excluded. All infants and mothers received the standard of care (a single dose of nevirapine at the time of delivery and seven days of infant prophylaxis using AZT). Infants were randomized to continue NVP prophylaxis from day 8 until week 14 while others were randomized to continue both AZT and NVP until week 14. At six months, the risk of HIV transmission was lower in both the extended NVP and extended AZT and NVP arms (4% vs 4.9%) compared to the standard of care (10.5%) *(10)*.

Extended postnatal prophylaxis for infants in the context of possible maternal viraemia

Six clinical trials in breastfed infants provided evidence on extended ARV prophylaxis beyond the first two months of life with five trials conducted before lifelong ART became the standard of care and only one trial conducted in the context of modern-day HIV treatment recommendations *(9–14)*. Two studies evaluated extended NVP prophylaxis in breastfed infants who tested HIV negative shortly after birth and born to mothers not on ART. One study compared the standard of care (a single dose of NVP for mother and infant at the time of delivery followed by a week of infant AZT prophylaxis) to extended infant prophylaxis using NVP alone or NVP+AZT for 14 weeks. At 12 months, both extended prophylaxis arms had lower rates of vertical transmission (6.3% vs 7.3%) and mortality (8.3% vs 8.7%) compared to infants who received only one week of ARVs (11.9% vs 10.4%). Another study compared the same standard of care to either maternal ART or infant NVP prophylaxis for 28 weeks or until the end of breastfeeding. At 48 weeks, there was no difference in postnatal transmission rates between the maternal ART arm and extended infant NVP arm (4%), and both were lower compared to the standard of care (7%) *(10,11)*.

A third study also compared maternal ART to extended infant NVP for 18 months or to the end of breastfeeding, and found that, in breastfed infants born to mothers not yet eligible for ART, HIV transmission at 18 months was < 1% and HIV-free survival at 24 months was similar in both arms *(16)*.

Another study compared six weeks of infant NVP prophylaxis to six months' prophylaxis in breastfeeding infants who tested negative for HIV at six weeks. In infants whose mothers were not on ART the risk of HIV transmission at 9 and 12 months was 2% and 2.8% in the extended NVP arm compared to 3.8% and 4%, respectively, among infants who discontinued NVP after six weeks *(18)*.

Two additional studies provided evidence on extended infant prophylaxis using an ARV other than NVP. A study in breastfed infants born to mothers not on ART evaluated lopinavir/ritonavir (LPV/r) or lamivudine (3TC) for 50 weeks or until the end of breastfeeding. In infants who had tested negative shortly after birth, extended ARV prophylaxis reduced the risk of postnatal transmission to 1.4% for LPV/r and 1.5% for 3TC. Similarly, at 50 weeks there was no significant difference in HIV-free survival, although there was a slightly higher risk of severe adverse events, in infants taking LPV/r *(15)*.

3TC was also evaluated as an extended infant postnatal prophylaxis in the context of maternal ART in another trial of infants whose mothers were found to have a VL ≥ 1000 copies/mL at the six-week or six-month immunization visit and were started on 3TC as postnatal prophylaxis for up to 12 months or one month after cessation of breastfeeding *(17)*.

Use of ARVs in neonates

In 2016, NVP, AZT, 3TC and LPV/r were the only ARVs available with an indication that includes their use in infants, although use of LPV/r was not advised below two weeks of age *(23)*. Since then, raltegravir (RAL) granules have been approved for use from birth and were included as part of the WHO-preferred ART regimens for neonates in 2016 [24).

More recently, data from clinical trials confirmed the safety of ABC in neonates and younger infants, which provided reassurance that ABC can be used as an option from birth onwards *(25,26)*.

The Guideline Development Group reviewed a study on the pharmacokinetics and safety of DTG in neonates *(27)* as well as a study from South Africa which investigated the dosing of ABC, 3TC and DTG using drug formulations that are widely available for paediatric treatment in low- and-middle-income countries *(28)*.

Both modelling and clinical trial data confirmed that, using a dispersible tablet formulation, DTG 5 mg administered every other day in the first two weeks of life achieves therapeutic and safe drug levels; however, it should be noted that the dose ought to be increased to 5 mg daily at two weeks of life until the infant is ≥ 4 weeks and weighs 6kg or more (see **Table 4.1**).

A dosing strategy for administering ABC/3TC 30/15 mg once daily, using a quartered dispersible tablet of 120/60 mg (double-scored) was found to achieve therapeutic levels at the upper limit of normal. In anticipation of using ABC/3TC with DTG in neonates, modelling demonstrated that the same dose of ABC/3TC 30/15mg, administered every other day in the first few weeks of life, could also achieve therapeutic levels *(28)*.

4.1.4 Rationale for the recommendation

Balance of effects

The recommendation to maintain six weeks of single-drug infant prophylaxis for all exposed infants is based on evidence that consistently demonstrates reduced intrapartum transmission risks and HIV infection rates < 1% by six weeks of age when maternal ART is combined with six weeks of single-drug ARV infant prophylaxis *(16)*.

The Guideline Development Group did not find evidence to support a shorter course of infant prophylaxis in this setting, due to the absence of studies directly comparing six weeks of infant prophylaxis to a shorter duration of or no prophylaxis in virally suppressed mothers. The Guideline Development Group's recommendation of NVP as preferred prophylaxis was based on established use for this purpose, with data showing that neonatal nevirapine demonstrates favourable tolerability with minimal severe adverse events. NVP can also be dosed once daily and is widely available both as a liquid formulation that enables accurate dosing and as a scored dispersible tablet available to deliver a 25 mg dose to older infants. The Guideline Development Group also considered the issue of potential ARV drug resistance if infant infection occurs. As NVP is no longer used for treatment, NNRTI resistance following use of NVP for infant prophylaxis should not compromise later DTG- or PI-based regimens.

Evidence on other drugs for infant prophylaxis is limited; consequently the Guideline Development Group was unable to find sufficient evidence to support them as preferred options. Evidence about the efficacy of both 3TC and LPV/r in the prevention of postnatal HIV infection is available from only one study *(15)*. 3TC is a relatively well tolerated drug and a suggested alternative option. LPV/r, while potent and effective, is poorly tolerated, expensive and the liquid formulation has handling requirements that require a cold chain: these factors make LPV/r suboptimal for this purpose given that there are alternative options.

There is no evidence about the efficacy of DTG when used specifically for infant prophylaxis. However, the Guideline Development Group considered that evidence on the benefits and harms of DTG as part of infant ART could be extrapolated to support its use as an option for infant prophylaxis.

In the smaller number of breastfeeding infants at higher risk of transmission (e.g. mothers who have not received ART or with proven viraemia), the Guideline Development Group recommended initial infant prophylaxis with three drugs for six weeks followed by single-drug prophylaxis until maternal viral suppression is documented or mothers have stopped breastfeeding. The initial three-drug regimen is given as "presumptive therapy", as these infants are at a higher risk of infection in utero or intrapartum. Once infant infection has been ruled out, single-drug prophylaxis provides additional protection until the mother achieves viral suppression on ART or until cessation of breastfeeding, whichever comes first.

Values and preferences of mothers living with HIV

An online survey conducted among caregivers found that when providing postnatal prophylaxis to their infant the primary consideration was effectiveness, with cost as the second most important factor. As part of a WHO-led series of consultations about postnatal prophylaxis, a peer-mother programme interviewed 20 women living with HIV and reported back on values, preferences and challenges faced in providing postnatal prophylaxis. Mothers reported finding it difficult to continue giving prophylaxis over a longer period of time and also mentioned that providing triple-drug or extended prophylaxis with multiple drugs for prophylaxis made some feel their child was already infected with HIV *(29)*.

Cost and cost-effectiveness

Multiple studies have found that HIV testing and treatment during antenatal care, lifelong maternal ART, and PrEP for pregnant and breastfeeding women are cost-effective both individually and at a population level in preventing vertical transmission. A modelling study in 2018 concluded that a combination of maternal regimen shift from efavirenz- to dolutegravir-based regimens and infant prophylaxis involving a six-week course of NVP, together with maternal peer support group, was the most beneficial and cost-effective set of interventions to achieve elimination targets in Zambia *(30)*.

Costs of specific ARV formulations vary by drug, duration of prophylaxis, mode of distribution and country licensing agreements. The formulations recommended by WHO for use as infant prophylaxis are available at a cost of US$1–2 per month *(31)*.

Acceptability and equity impact

Challenges with risk stratification have resulted in some programmes opting to treat all HIV-exposed infants as high risk. The Guideline Development Group determined that further efforts should be made to improve the feasibility of risk stratification. The strategy of recommending universal enhanced prophylaxis leads to unnecessary drug exposure in most neonates who are, in fact, at low risk of HIV acquisition.

Feasibility

Drug selection and availability impact the feasibility of delivering postnatal prophylaxis. Liquid formulations for single drugs provide flexible dosing options but are bulky and relatively more costly for supply chains to manage. Easier-to-use formulations such as dispersible scored tablets may be easier and less expensive for programmes and caregivers, but the dosage may not be appropriate for use in neonates and care must be taken if using this approach.

Additionally, ensuring feasibility requires ongoing availability of NVP which is now infrequently used for treatment and may therefore be deprioritized by manufacturers over time. It is essential for programmes to quantify and communicate their demands to manufacturers in order to maintain production.

Conclusions

The Guideline Development Group considered the risk-benefit ratio of prophylaxis options including evidence on efficacy, safety and feasibility using ARVs that are readily available. To simplify the recommendation for infants not at high risk of HIV infection, the Guideline Development Group strongly recommends six weeks of single-drug prophylaxis with higher certainty of evidence for NVP compared to the alternatives 3TC and DTG. For infants at high risk of HIV infection, the Guideline Development Group makes a strong recommendation for six weeks of triple-drug ARV-enhanced prophylaxis despite low certainty of evidence, with a preference for ABC, 3TC and DTG- containing regimens, while taking into consideration concerns that mothers living with HIV may have about giving ARVs to their infants. For breastfeeding infants, the Guideline Development Group also makes a strong recommendation that six weeks of a triple-drug regimen should be followed by extended prophylaxis using a single drug until maternal viral suppression is attained or breastfeeding is concluded.

4.1.5 Implementation considerations

Risk stratification remains essential to limiting unnecessary drug exposure. In settings where access to maternal viral load availability is unreliable, adopting a simpler means of assessing risk such as maternal time on ART may need to be further emphasized and reinforced in health worker training. Adherence support for breastfeeding mothers is also a critical intervention to support daily adherence to treatment and maintain retention in care, as well as to remind mothers of the infant-testing schedule.

When an infant at high risk of infection is identified, a blood sample should be taken and sent for nucleic acid testing (NAT). It is important to ensure that mothers are adequately counselled so that they understand the rationale for a three-drug regimen which serves as both enhanced prophylaxis and presumptive treatment until HIV infection can be ruled out. Maternal ART should also be initiated or reinitiated at the time, as required. All efforts should be made to obtain an infant blood sample for NAT testing with return of test results within six weeks. If the test turns out to be negative, HIV prophylaxis may be stopped completely if maternal viral suppression can also be confirmed, or if there is reasonable assurance of maternal adherence to treatment. However, if the NAT test is negative but there is concern that maternal viral suppression has not been attained, prophylaxis should be maintained using a single ARV, with a preference for NVP.

If the triple-drug regimen used for neonates is ABC+3TC+DTG, appropriate caution should be exercised depending on the formulation used. DTG must be dosed once every other day, or every 48 hours from birth until two weeks of life, after which dosing is once daily. At one month, dosing should then be adjusted based on the infant's weight (see **Table 4.1**). The triple-drug fixed-dose combination of ABC, 3TC and DTG (known as "pALD") is not appropriate for use in neonates but may be used in infants older than four weeks. Careful attention must be given to maternal counselling and supportive interventions to ensure that the right dosing schedule is followed and dosing can be adjusted as appropriate.

Table 4.1 Simplified dosing of ABC, 3TC and DTG for neonates and infants

Drug	Strength of paediatric formulation	Neonate (< 4 weeks)		Infant (> 4 weeks)	
		Dose by age (in weeks)		Dose by weight (in kg)	
		0 to < 2 weeks[a]	2 to < 4 weeks	3 to < 6 kg	6 to < 10 kg
ABC/3TC[a]	Double-scored tablet (dispersible) 120 mg/60 mg[#]	¼ tablet (every other day)	¼ tablet (every day)	½ tablet (every day)	1 ½ tablet (every day)
DTG	Tablet (dispersible) 5 mg	1 tablet (every other day)	1 tablet (every day)	1 tablet (every day)	3 tablets (every day)
	Tablet (dispersible) 10 mg	½ tablet (every other day)	½ tablet (every day)	½ tablet (every day)	1 ½ tablet (every day)
ABC/DTG/3TC	Tablet (dispersible) 60/30/5 mg	-	-	1 tablet (every day)	3 tablets (every day)

a. Abacavir/lamivudine (ABC/3TC) and DTG should be administered every other day for the first 2 weeks of life; on reaching age 2 weeks, neonates can receive the same dose of (ABC/3TC) and DTG once daily. In the first two weeks of life, the dosing interval does not need to be exactly 48 hours, but an effort should be made to administer the dose at a consistent part of the day (e.g. in the mornings or in the evenings). It is important to note that there are two versions of ABC/3TC (120 mg/60 mg) dispersible tablets made by different manufacturers: one version is double-scored, and the other only single-scored. It is critical that only the double-scored tablet be used when administering the neonatal dose of one quarter of a tablet *(8, 32-34)*.

#. It is recommended that the caregiver be provided with support interventions, such as a dosing calendar, to facilitate appropriate dosing and dosing adjustments.

Programmes should monitor infant prophylaxis regimens and formulations dispensed in order to support quantification efforts. At the global level this will provide clear messaging to suppliers on those products that are still required.

4.1.6 Research gaps

The Guideline Development Group discussed and identified research gaps that underscore the complexity of optimizing infant prophylaxis in the context of preventing mother-to-child transmission.

Safety and toxicity of triple-drug ARV regimens in neonates, including preterm and low-birth-weight infants. There is limited evidence on the safety profile of triple-drug ARV regimens in neonates, especially among preterm and low-birth-weight infants who are physiologically more vulnerable. The development of novel dosing strategies for available ARVs is still needed for preterm infants, and long-term observational cohorts may provide data on longer term safety.

Concerns regarding persistent NNRTI resistance. There is ongoing debate about whether NNRTI resistance remains a significant concern in the context of infant prophylaxis using NVP. Surveillance studies documenting high rates of NNRTI resistance were largely completed prior to the global rollout of DTG-containing treatment and may not reflect the current population-level persistence of NNRTI resistance.

Risk stratification and duration of prophylaxis. Studies are needed to reassess how infant risk is defined, especially in the context of improved maternal regimens that are potent and can rapidly reduce viral load. There is also a need to explore whether shorter durations of prophylaxis may be safe and effective in specific low-risk scenarios, thereby reducing drug exposure and potential toxicity.

Challenges in conducting clinical trials. With vertical transmission rates now very low in many settings and standards of care highly variable, conducting traditional RCTs to assess infant prophylactic strategies is increasingly difficult. New methodologies or adaptive trial designs may be required to generate evidence in a feasible and cost-effective manner while still maintaining scientific rigour.

Acceptability and feasibility of dolutegravir (DTG)-dosing regimens. The potential use of once-every-other-day dosing of DTG during the first two weeks of life requires further exploration. Research is needed to assess the acceptability of caregivers, feasibility of implementation in real-world settings and clinical efficacy in neonates during this sensitive period. Addressing these questions through targeted research will be essential to refine global guidance, improve infant outcomes and move closer to the elimination of paediatric HIV.

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4.2 HIV and infant feeding

4.2.1 Recommendations

Recommendations (2016) *(1)*

Duration of breastfeeding by mothers living with HIV[a]: mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or longer (as for the general population) while being fully supported for ART adherence.
strong recommendation, low certainty of evidence for 12 months; very low certainty of evidence for 24 months[b]

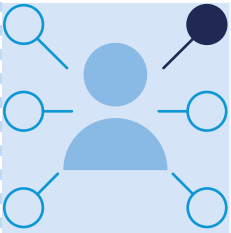
Remarks

In settings in which health services provide and support lifelong ART, including adherence counselling, and promote and support breastfeeding among women with HIV, the duration of breastfeeding should not be restricted. Furthermore, as for the general population, mothers living with HIV (and whose infants are HIV uninfected or of unknown HIV status) should exclusively breastfeed their infants for the first six months of life, introducing appropriate complementary foods thereafter while continuing to breastfeed.

Breastfeeding should then only stop once a nutritionally adequate and safe diet without breast milk can be provided.

a. This recommendation updates the component of the 2010 recommendation relating to breastfeeding practices and the duration of breastfeeding. The components of the 2010 recommendation on breastfeeding practices and stopping breastfeeding remain unchanged and valid.

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



Recommendation (2025)

In settings where the national programme recommends replacement feeding: mothers living with HIV who are receiving ART and virally suppressed should be offered the choice of breastfeeding and supported in their infant feeding choice.
strong recommendation, low certainty of evidence

Recommendation (2025)

Offer enhanced community- and facility-based interventions to support mothers living with HIV who are breastfeeding in order to optimize ART adherence, improve retention of mother-and-infant pairs in care and optimize breastfeeding.
conditional recommendation, very low certainty of evidence

4.2.2 Background

Breastfeeding is a cornerstone of child survival, nutrition and development, especially in the first year of life. Breastfeeding – especially early and exclusive breastfeeding – has benefits for infants which include promoting growth and neurocognitive development, preventing malnutrition and infectious diseases, and improving neonatal and infant survival rates *(2–6)*. Studies have also demonstrated that early weaning increases morbidity and mortality in infants exposed to HIV *(7)*. The benefits of breastfeeding go beyond the early years in both low- and high-income countries, a major benefit being a reduced risk of obesity and chronic disease in later life *(7–10)*. In addition to the benefits for children, there are short- and long-term health benefits for breastfeeding mothers such as a reduced risk of breast and ovarian cancers *(11)*.

However, breastfeeding by mothers living with HIV carries a risk of infection for their infants *(12,13)*. The mechanisms by which HIV transmission occurs through breastfeeding remain incompletely understood although the risk increases at a higher maternal viral load, for instance if mothers experience incidental HIV infection during breastfeeding, in the absence of ART or with suboptimal ART adherence. Since 2013, WHO has recommended that all mothers living with HIV receive life-long ART to support their health and ensure the well-being of their infants.

Scaling up interventions such as increased maternal HIV diagnosis, better access to maternal ART during pregnancy and breastfeeding, and wider use of infant antiretroviral prophylaxis have significantly reduced the risk of vertical HIV transmission in breastfeeding populations *(14–17)*. In 2010, WHO issued its first public health recommendation: national authorities should promote and support a single infant-feeding practice among all mothers living with HIV attending public health facilities. It also recommended that this decision should be taken at a national level after taking into consideration local HIV and general maternal and child health epidemiological and systemic factors. Commercial infant formula was only to be given if specific conditions could be met to ensure that replacement feeding was acceptable, feasible, affordable, sustainable and safe. In settings where diarrhoea, pneumonia and undernutrition were common causes of infant and child mortality, breastfeeding was most likely to improve HIV-free survival among HIV-exposed infants. This recommendation was subsequently updated: in programmes promoting breastfeeding, mothers living with HIV who were on ART and adherent to treatment were encouraged to breastfeed exclusively for the first six months, and then combine breastfeeding with complementary foods until 12 months *(18)*, with the possibility of continuing breastfeeding up to 24 months of age or until a nutritionally adequate and safe diet could be provided *(1)*. ART adherence is critical to achieving and maintaining viral suppression among pregnant and breastfeeding women with HIV. Suboptimal adherence can lead to viral nonsuppression and ARV drug resistance, thereby increasing the risk of vertical HIV transmission. Retention in care and sustaining ART adherence throughout pregnancy and breastfeeding remain challenging. Several factors have been identified as being associated with poor retention: nondisclosure of HIV status, stigma, partner violence, food insecurity, depression and ARV drug-related challenges *(19–22,23)*.

Despite solid evidence indicating that there is a reduced risk when maternal viral suppression is sustained, in low- and middle-income countries where breastfeeding is the infant feeding method promoted by health authorities, ongoing fears about the risks of transmission during breastfeeding may contribute to reluctance or discouragement to breastfeed and result in unsafe or inappropriate replacement feeds *(24,25)*. Studies conducted in high-income countries have also shown that despite national guidelines advising against breastfeeding, some women living with HIV still desire to breastfeed and will in fact choose to do so if national policy allows it. This inconsistency between national guidelines and women's desires disempowers health care providers who seek to support infant feeding decisions by women with HIV. More worryingly still, there have been reports of the criminalization of women with HIV who choose to breastfeed *(26–30)*.

4.2.3 Evidence summary

Postnatal transmission

In a recent systematic review and meta-analysis to quantify the relationship between maternal viral load and postnatal HIV transmission, no study was found that directly compared the risk of vertical transmission with breastfeeding versus replacement feeding of infants born to mothers with HIV and virally suppressed on ART. Evidence on the risk of HIV transmission in relation to the maternal viral load may provide some indirect evidence to guide breastfeeding decisions in this situation. A systematic review and meta-analysis showed that postnatal HIV transmission was strongly associated with higher maternal HIV viral load *(31)*. However, there have also been rare instances of transmission during breastfeeding even with documented maternal viral loads < 50 copies/mL *(32–35)*. This is consistent with rare reports of postnatal transmission in the context of an undetectable maternal viral load in serum and/or breastmilk, and may be due to infectious, cell-associated virus in breastmilk *(32,35,36)*. Dissimilar reporting of infant postnatal prophylaxis in the studies included in the systematic review made it difficult to directly assess the importance of the role of infant prophylaxis in reducing the risks of postnatal HIV transmission during maternal virological suppression. Furthermore, these studies largely took place prior to the widespread availability of INSTI-based ART and more robust PI-based (i.e. atazanavir- or darunavir-based) regimens: the risk of postnatal transmission in the context of maternal virological suppression with currently recommended ART regimens therefore remains unclear. The finding of a very low (< 0.1%) monthly risk of postnatal transmission when maternal viral load of < 50 copies/mL provides indirect evidence to support breastfeeding in the context of maternal HIV with viral suppression *(37)*. However, more data are needed from studies in which breastfeeding women are monitored frequently (i.e. monthly or more often) and maternal ART regimens and infant prophylaxis use are clearly documented to further assess transmission during breastfeeding. It is noteworthy that an “undetectable” viral load threshold differs between studies, varying from < 20 copies/mL to < 50 copies/mL, < 300 copies/mL or even < 400 copies/mL.

Support interventions for breastfeeding women with HIV

A systematic review and meta-analysis of eight randomized trials conducted between 2008 and 2020 assessed interventions (peer support, health care support, nutritional support, remote support and integrated mother and child health interventions) to support breastfeeding among mothers living with HIV. Two studies showed a moderate increase in the likelihood of viral suppression and a small increase in exclusive breastfeeding and no difference in retention when health care support (defined as facility-based interventions involving HIV or MCH providers) was compared to standard of care *(38,39)*. There was a small increase in the likelihood of exclusive breastfeeding but no difference in the likelihood of retention in care with peer support (community- or facility-based interventions involving peer mothers or other providers not formally trained in HIV or MCH) compared to standard of care in four studies *(40–43)*. Nutrition support and remote interventions did not show any difference in the likelihood of breastfeeding or retention compared to standard of care in three studies *(40,44,45)*. Overall, most differences between specific breastfeeding support interventions and standard of care were not statistically significant except for a moderate increase in viral suppression with support. When all support interventions were considered together, there was a modest but statistically significant increase in the likelihood of exclusive breastfeeding but not of retention. It is, however, important to note the difficulties involved in combining different types of support interventions, and there were several limitations including risk of bias, inconsistency and imprecision leading to low and very low level certainty of evidence based on the GRADE classification *(46)*. These randomized control trials of support interventions were not designed to address harms although, given the nature of the interventions, no serious harms were to be expected.

4.2.4 Rationale for the recommendation

Benefits and harms

No study directly compared the risk of infant transmission with breastfeeding versus replacement feeding in infants born to mothers with HIV who were virally suppressed on ART. However, a systematic review *(47)* found very low rates of transmission to breastfeeding infants when maternal viral loads were undetectable. The benefits of breastfeeding have been well described.

A systematic review that summarized the support interventions for breastfeeding among women with HIV *(46)* indicates their benefits, with minimal harms, in the following cases: health support, peer support and all support interventions combined. Nutritional support and remote interventions were not associated with clear benefits.

Values, preferences and acceptability

Studies in settings where replacement feeding is recommended show that some women with HIV want to discuss options for infant feeding and may prefer to breastfeed their children if they are virologically suppressed *(48)*. Mothers value breastfeeding for the health benefits it offers their infants; for mothers themselves, not breastfeeding may increase stigma and have negative psychological experiences and cultural consequences *(48–51)*. Replacement feeding with commercial infant formula milk may be considered artificial and unnatural and associated with stigma, as formula feeding itself can single out mothers living with HIV as being HIV-infected *(49–51)*. Qualitative studies describe several factors which facilitate breastfeeding among women with HIV, e.g. provision of appropriate, objective and impartial information, the option of making an informed infant feeding choice as well as empowerment and support of autonomy in decision-making and infant-feeding practices *(52,53)*. Nevertheless, many women – especially in high-income settings – may still prefer replacement feeding to avoid any risk of transmission or for other reasons.

Other published reports describe the values and beliefs of providers in support services working with mothers living with HIV who breastfeed. Some studies find that providers have difficulty undertaking breastfeeding discussions with mothers living with HIV. In contrast, clear patient care guidelines and institutional protocols grounded in risk reduction and respect of patient autonomy can help providers to deliver appropriate counselling and support services. Provider workload and inadequate training are challenges that managers need to address in order to assist health professionals to deliver the needed support *(54–56)*.

When women with HIV are provided with adequate information and opportunities for an informed decision, they consider breastfeeding desirable and acceptable against a background of very low infant transmission rates *(57)*. Personalized infant-feeding support interventions, family-centred support interventions, tailored adherence counselling support, peer support interventions, personalized and content-neutral remote interventions are all highly acceptable to breastfeeding mothers living with HIV in different settings *(52,58–62)*.

Feasibility, cost and cost-effectiveness

As is the case with mothers not living with HIV, breastfeeding is always feasible even if some women experience difficulties such as a perceived milk insufficiency, trouble achieving a good latch or for other, work-related reasons. Facility- and community-based interventions are practicable and effective, although they need to be tailored to the demands of mothers living with HIV *(58,63)*.

Two modelling studies examined the cost-effectiveness of different infant-feeding options for mothers living with HIV in Canada and South Africa and found that exclusive breastfeeding was more cost-effective than exclusive formula feeding *(64,65)*. These analyses considered direct costs, lifetime costs to the health system, HIV-free survival, morbidity and mortality related to infant feeding and disability-adjusted life years (DALYs) averted.

The cost and cost-effectiveness for individual and combined support interventions will vary depending the socioeconomic and geographical contexts. While there is limited evidence for generalizability, modelling studies have shown that some interventions (e.g. peer support groups) may be cost-effective *(66,67)*.

Equity

Recommendations prohibiting breastfeeding in the context of HIV and coercive legislation founded on potential HIV transmission via breastfeeding disadvantage women living with HIV and exacerbate stigma, discrimination and social exclusion. Provision of additional support services to already disadvantaged women with HIV and their infants, who may be impacted by existing socioeconomic, cultural and racial disparities, may contribute towards increased health equity. Health status, income, and availability of food and family support all have an influence on the infant-feeding practices of mothers living with HIV. Lack of available resources and information may inadvertently contribute to poor health outcomes among vulnerable infants and women and deepen disparities in health. Additional support, resources and information could lead to improved health and economic outcomes, especially for families with socioeconomic vulnerability *(63,68–70)*.

Conclusion

Postnatal transmission

Despite the low certainty of evidence, the Guideline Development Group decided to issue a strong recommendation based on the low risk of HIV transmission through breastfeeding when mothers are on ART and virally suppressed. The Guideline Development Group agreed that this evidence supports updating WHO guidance to encourage a woman-centred counselling and care approach for women living with HIV who express a desire to breastfeed. In settings where the risk of infant and young child morbidity and mortality from malnutrition and infectious disease is high, WHO already recommends breastfeeding in mothers living with HIV who are receiving maternal ART and infant postnatal prophylaxis. This recommendation has been widely adopted in many national and subnational programmes and has improved child survival rates *(4,71,72)*. Considering the low risk of vertical transmission when maternal ART is highly effective, the Guideline Development Group agreed that there is no justification for mothers living with HIV to be excluded from this feeding option in countries where breastfeeding is not the national recommendation for women living with HIV. Instead, these women should have access to updated, accurate information about the risk of HIV transmission through breastfeeding to facilitate their decisions on infant feeding.

Support interventions for breastfeeding women with HIV.

The Guideline Development Group made a formal recommendation that support interventions should be provided to breastfeeding women living with HIV to support adherence and optimal breastfeeding. Although these interventions are generally acceptable and feasible, the recommendation was conditional since implementation will be highly dependent on the mother's setting and circumstances, and evidence to define a standard combination package of interventions is limited. Studies in the general non-HIV population confirm that breastfeeding support and education provided by professionals and peers to individual women, including support delivered remotely, are associated with an increased duration of any and exclusive breastfeeding *(73)*.

4.2.5 Implementation considerations

Ministries of Health, together with their partners, need to prioritize efforts to protect, promote and support breastfeeding in all settings in the general population; they also need to create and sustain enabling environments that promote appropriate infant-feeding practices while scaling up interventions to reduce HIV transmission. In all circumstances, it is critical to provide mothers living with HIV and their communities with high-quality, accurate information about HIV transmission and breastfeeding. To help mothers make informed decisions about their infant-feeding choices, free of coercion or intimidation, health care providers need to be trained and equipped to provide clear, concise communication about breastfeeding in the context of maternal HIV (see **Box 4.1** for specific capacity-building areas).

Box 4.1 Capacity-building topics for health care providers to support breastfeeding among women with HIV

- Short- and long-term health benefits of breastfeeding as well as its importance for infant growth, development and lifelong health, e.g. importance of breastfeeding in settings where there is an increased risk of malnutrition, diarrhoeal and infectious diseases owing to its effect on reducing morbidity and mortality.
- Health benefits of breastfeeding for mothers.
- Importance of early initiation of ART and maintaining adherence to achieve viral suppression before and during pregnancy and breastfeeding.
- Value of suppressing viral loads to reduce the risk of postnatal HIV transmission.
- Considerations for viral load monitoring throughout breastfeeding in accordance with national guidelines.
- Importance of adhering to infant ARV prophylaxis in accordance with national recommendations.
- Sources of practical support for breastfeeding mothers living with HIV in the event of difficulties.

It is important for national programmes to prioritize strategies to scale up HIV testing and retesting, ensure access to antiretrovirals for treatment and prophylaxis, and provide ART adherence support services with optimized viral load monitoring for pregnant and breastfeeding women (see **Box 4.2** for specific programme strategies).

Box 4.2 Programme strategies to support breastfeeding among women with HIV

- Integrating HIV and RMNCAH services in all settings to promote access, including breastfeeding counselling and support, ART adherence support and retention in care and linking them with other key health care contacts, e.g. infant feeding review and counselling on infant testing.
- Providing breastfeeding support that is consistent across policies and programmes, health facilities and community activities for all women, including mothers living with HIV, to create an enabling environment for this practice, not only on beginning and during the exclusive breastfeeding period, but also enabling mothers to breastfeed for longer, i.e. until 24 months or beyond.
- Promoting comprehensive person-centred care and support during the postnatal period including addressing postpartum depression and other psychosocial needs.
- Implementing an optimized postnatal prophylaxis approach for infants exposed to HIV based on current recommendations *(see Section 4.1 on postnatal prophylaxis).*
- Implementing HIV retesting policies for HIV-negative pregnant and breastfeeding mothers at risk of HIV infection with provision of appropriate pre-exposure prophylaxis (PrEP) or early ART in the event of maternal HIV infection.
- Strengthening data collection, monitoring and evaluation of infant feeding practices, breastfeeding duration, infant prophylaxis and infant testing including final diagnosis and maternal viral load results to improve quality of service.
- Safeguarding a supportive environment for mothers who opt to breastfeed, protecting them from coercion, stigmatization, intimidation and criminalization.
- Encouraging community engagement and service delivery approaches to generate support for appropriate infant feeding practices in line with a woman's rights to make informed choices, to address barriers to breastfeeding and to help community service providers to support breastfeeding more effectively in their communities.
- Developing and strengthening facility- and community-based approaches (including individual and group adherence support, follow-up and peer programmes) and linking them to other services, e.g. legal, social and economic provisions to address barriers to ART retention and adherence, postnatal prophylaxis and recommended infant feeding practices. Programmes ought to establish the most cost-effective approach in order to ensure that the intervention delivery model is sustainable.

4.2.6 Research gaps

Research gaps were identified by a group of technical experts involved in the development of the guideline and by the Guideline Development Group.

Maternal ARV regimens. There is limited evidence on the HIV transmission risk for women with HIV on current INSTI-based and PI-based regimens. Important topics for future evaluation include the postnatal HIV transmission risk among infants of breastfeeding women on DTG-based regimens, optimal ARV regimens to ensure maternal viral load suppression during breastfeeding and optimal viral load monitoring for breastfeeding women with HIV.

Infant postnatal prophylaxis. There is also limited evidence on the HIV transmission risk for infants on recommended postnatal ARV prophylaxis. Studies are needed to determine the duration and optimal postnatal prophylaxis for infants exposed to HIV that would provide greater confidence in support for breastfeeding and HIV testing strategies for infants during breastfeeding.

Impact on HIV-exposed infants. The clinical effects (early and late health outcomes, especially growth) of long-term infant exposure to low-dose ARV drugs in breast milk remain unclear. Additionally, the effects of maternal ART on renal and bone metabolism and nervous system development in breastfeeding HIV-exposed infants need to be further studied.

Needs and interventions to support breastfeeding among women with HIV. There is also a lack of clarity concerning the optimal or ideal support intervention packages for breastfeeding women with HIV. Future research should focus on barriers to breastfeeding in settings where replacement feeding is recommended; interventions that support initiation and sustained breastfeeding among mothers with HIV who are receiving ARV drugs including under special circumstances like work and school; implementation of rights-based approaches; and the effect of interventions that aim to increase exclusive and continued breastfeeding, retention in care and promote infant growth, development and survival in all settings.

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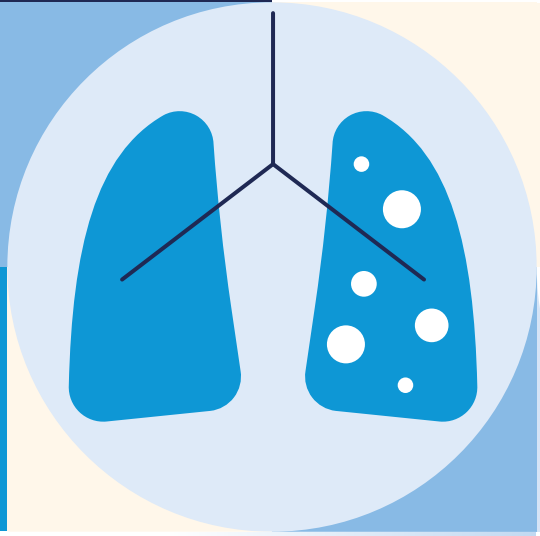
05

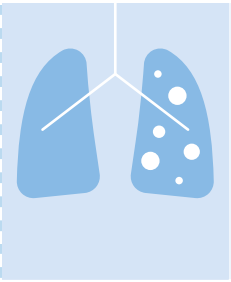
Tuberculosis prevention in people living with HIV



5. Tuberculosis prevention in people living with HIV

5.1 Preferred TB preventive treatment regimens for people living with HIV

5.1.1 Recommendation



Recommendation 2025

In adults and adolescents with HIV eligible for tuberculosis preventive treatment (TPT), three months of weekly isoniazid + rifapentine (3HP) is the suggested preferred regimen; six or nine months of daily isoniazid (6H or 9H) are alternative regimens.*

conditional recommendation, low certainty of evidence

*considering and complementing existing recommendations on TPT regardless of HIV status *(1)*

5.1.2 Background

Tuberculosis (TB) remains the leading cause of mortality among people living with HIV (PLHIV), with an estimated 150 000 deaths reported globally in 2024 *(1)*. TB preventive treatment (TPT) has consistently demonstrated a significant reduction in both TB incidence and TB-related mortality among PLHIV. Historically, longer regimens such as six or nine months of daily isoniazid (6H/9H) have been widely used but are associated with low treatment adherence and increased toxicity. Recognizing these challenges, WHO updated its guidance for TPT for people regardless of HIV status to include shorter rifapentine-based regimens such as 1HP (one month of daily isoniazid and rifapentine) and 3HP (three months of weekly isoniazid and rifapentine) as additional options to six or nine months of daily isoniazid *(2)*. Despite WHO recommendations for shorter rifapentine-based regimens, uptake among people living with HIV in LMICs remained low by 2023 *(1)*. There is growing global consensus on the need to prioritize shorter TPT regimens to meet the global goals of ending TB and AIDS as a public health threat by 2030. These global efforts should focus on improving access, aligning choices with client preferences, addressing comorbidities and contraindications, and mainstreaming implementation for broader programmatic impact. Importantly, the global scale-up of antiretroviral therapy (ART) has shown that simplifying regimens, standardizing care and applying a public health approach can dramatically improve treatment access, adherence and outcomes while reducing costs and health system burden. Building on these lessons, optimizing TPT for people living with HIV by prioritizing the use of fewer preferential highly effective, shorter-course regimens can enable similar gains – supporting more efficient implementation, improved uptake and ultimately greater impact in preventing TB in this population.

5.1.3 Supporting evidence

Use of shorter TPT regimens in adults and adolescents living with HIV

A systematic review and meta-analysis conducted to support this guideline assessed the effectiveness and safety of shorter-course TPT regimens among PLHIV. This review included 20 studies, including 13 randomized controlled trials (RCTs) and seven prospective observational studies, covering 12 731 participants *(3)*. Treatment completion rates were significantly higher for 1HP (97%; 95% CI: 96–98%) and 3HP (92%; 95% CI: 90–94%) compared to 6H (72%; 95% CI: 62–82%). Grade 3 and 4 adverse events were reported at lower rates for 3HP (5%; 95% CI: 0–10%) and 1HP (7%; 95% CI: 0–15%), in contrast to 6H

which had a 15% incidence of serious adverse events (95% CI: 3–26%). Hepatotoxicity was also reduced in the shorter regimens: 3HP was associated with a 0% incidence (95% CI: 0–1%), 1HP with 2% (95% CI: 2–3%), and 6H with 4% (95% CI: 1–7%). TB incidence and mortality were lower with 3HP and 1HP, although differences were not statistically significant *(4–9)*.

An earlier 2021 systematic review and network meta-analysis including 16 RCTs highlighted that rifamycin-containing regimens (3HP, 3HR, 1HP) had better completion and safety outcomes compared to isoniazid-only regimens (6H, 12H, 36H), with no evidence of increased drug resistance. These regimens were found to be at least as effective at preventing TB and were associated with lower mortality risk in PLHIV *(10)*. Data from a phase 3 trial in Thailand further suggest that 1HP co-administered with once-daily TLD is well tolerated and effective in maintaining virological suppression, although data for 1HP use in people on ART in populations from other global regions are limited *(11)*.

Use of shorter TPT regimens in special populations of people living with HIV

Both 3HP and 1HP regimens are compatible with dolutegravir-based ART, supporting viral suppression with adjusted ART dosing, including potential compatibility in pregnancy *(12)*. Recent data shows that 3HP may be safely co-administered with dolutegravir-based ART in ART-naïve individuals without dose adjustments *(13)*. However, evidence on the use of shorter-course regimens in pregnancy remains sparse and inconclusive. Current evidence does not support the routine use of 1HP in pregnancy due to limited safety data, the need for complex ART adjustments (e.g. twice-daily dolutegravir), a higher incidence of adverse events compared to 3HP and the absence of data on first-trimester exposure *(1,12,14,15)*. 3HP is supported by limited (phase 2 RCT) evidence as a safe and pharmacokinetically appropriate TPT option in pregnant women living with HIV on dolutegravir, with once-daily DTG dosing. These findings are encouraging yet remain preliminary. Broader use in pregnancy (including HIV-negative women and first trimester exposure) still requires additional research *(12)*.

TPT is recommended for all children living with HIV and for child household contacts of TB cases *(16)*. Safety and dosing for 3HP have been validated in young children, providing information on paediatric dosing *(17)*. The availability of a child-friendly 3HP dispersible formulation represents an important step towards improved adherence and programmatic uptake. 1HP is recommended only for adults and adolescents (≥ 13 years). There is not enough evidence to support 1HP use in younger children. Regimen selection and dosing adjustments are required when co-administering TPT with ART in children owing to concern about drug-drug interactions (DDI) between rifamycins (rifampicin, rifapentine) and antiretrovirals, particularly dolutegravir (DTG), lopinavir/ritonavir (LPV/r) and protease inhibitors (PI).

5.1.4 Rationale for the recommendation

Certainty of evidence

The certainty of evidence on TPT completion was rated as very low, primarily due to substantial differences in how completion was measured and concerns regarding indirectness. The certainty of evidence for other outcomes – including grade 3 and 4 adverse events, hepatotoxicity, TB incidence and HIV viral load suppression – was considered low due to limitations in study design, potential risk of bias and imprecision in effect estimates. There were few deaths in these studies. Despite these limitations in certainty, the overall direction of the evidence consistently favours the use of shorter regimens, especially 3HP and 1HP, over the traditional 6H regimen *(3)*.

Balance of effects

The balance between desirable and undesirable effects favours the use of shorter-course regimens. Both 1HP and 3HP show better adherence and lower toxicity profiles compared to 6H. While 1HP may involve some ART adjustments, the overall impact is manageable, especially with structured counselling and monitoring *(3)*. It is important to support adherence during pregnancy in order to avoid subtherapeutic ART levels *(9)*.

Values

A values and preferences survey conducted for this guideline confirmed that PLHIV prioritize treatment simplicity, minimal side-effects and regimen flexibility. Weekly dosing and lower pill burden made 3HP particularly popular, while the shorter duration of 1HP was also valued. Studies in Uganda and Kenya reaffirmed these findings, noting broad support for 3HP even in resource-limited settings *(18,19)*.

Resource use, cost and cost-effectiveness

Modelling shows that 3HP is the most cost-effective regimen overall, estimated at approximately US$722 per DALY averted, with an average cost per course of US$9.99. 1HP, although more expensive (approximately US$20 per course), remains cost-effective where feasible *(20)*. Shorter-course TPT is more

efficient in the long term due to fewer clinic visits and improved adherence. There are additional costs due to services such as vitamin B6 supplementation for any INH-containing regimen and client support, but these are inexpensive and have been shown to improve treatment outcomes. Global procurement platforms have reported consistent reductions in regimen costs through generic procurement and policy interventions *(20,21)*. Additionally, cost and manufacturing data have shown a decrease in the price of 3HP from US$72 in 2017 to US$9 in 2023 *(22)*, and its fixed-dose formulation has been included in the WHO Essential Medicines List since 2023 *(23)*. These developments have markedly increased availability, with global rifapentine production rising from 180 000 courses in 2018 to over 4.5 million courses by 2023 *(24,25)*.

Acceptability and equity

Both rifapentine-based shorter regimens – 3HP and 1HP – have demonstrated high acceptability among people living with HIV. Equity is likely to be enhanced as shorter-course regimens improve overall access to care and treatment completion in marginalized populations. Studies show no significant preference variation across age, education or poverty indices *(18)*. Kenyan data indicate strong uptake among people with advanced HIV disease *(19)*.

Feasibility

Implementation feasibility is high for 3HP, which is already integrated in national programmes and available as a fixed-dose combination. 1HP may be feasible with ART monitoring, particularly where dolutegravir-based regimens are used.

Evidence from the 2021 3HP Options Trial in Uganda showed that 92.9% of participants completed 3HP under flexible care models, regardless of demographic factors when delivered through tailored strategies *(26)*.

Conclusion

The Guideline Development Group recommended 3HP as the preferred shorter-course TPT regimen for people living with HIV. This is based on its favourable balance of clinical effectiveness, safety profile and high completion rates. 3HP is also compatible with WHO-recommended preferred ART regimens (with no need for dose adjustments), being available at lower cost and with broader availability across country programmes, including as a fixed-dose combination. 1HP is also supported by evidence indicating strong efficacy and high completion. However, 1HP has a higher cost and there is insufficient data on its use in special populations, including pregnant women and children under two years of age. 1HP remains a promising alternative option where feasible and, as more safety and feasibility data become available, it could be considered for future guidance. Although 6H/9H regimens remain widely used due to their low cost and broad accessibility, these regimens are associated with low completion rates and higher toxicity compared to shorter-course alternatives. 6H/9H regimens are still available as alternative options in some national programmes. Based on clinical and programmatic considerations, other WHO-recommended regimens – such as 3HR, 1HP, 4R and 6Lfx – are proposed for use in special circumstances (**Table 5.1**). Overall, a preferential approach to TPT for PLHIV – prioritizing short, effective, and scalable regimens – aligns with global best practices and lessons from ART scale-up.

Table 5.1 TPT regimens in people living with HIV

Population	Preferred	Alternative	Other (special circumstances)
Adults and adolescents	3HP (isoniazid + rifapentine weekly for 3 months)	6H (isoniazid daily for 6 months)[1] 9H (isoniazid daily for 9 months)[2]	1HP (isoniazid + rifapentine daily for 1 month)[3] 3HR (isoniazid + rifampicin daily for 3 months)[4] 4R (rifampicin daily for 4 months)[5] 6Lfx (6 months of daily levofloxacin)[6]

1. Acceptable where rifapentine-based regimens are not feasible.

2. Given long treatment duration and risk of poor adherence, may require adherence support.

3. 1HP not approved for children < 13 years old; potential ART interaction.

4. To not use with PIs, NVP, DOR; caution when used with TAF; adjust dose with DTG, RAL; often used in children with HIV.

5. Acceptable if other regimens are not available and for people on ART-compatible regimens (e.g. EFV-based).

6. For people living with HIV exposed to multidrug-/rifampicin-resistant TB in all settings, subject to certain conditions.

5.1.5 Implementation considerations for scaling up shorter TPT regimens in PLHIV

Successful implementation of TPT in people living with HIV requires a comprehensive approach across multiple programmatic areas. National programmes may prioritize the use of 3HP as the preferred regimen in people living with HIV. While a preferential recommendation is beneficial, national programmes must still maintain access to alternative recommended options such as 6H/9H, and enable the use of 1HP, 3RH and 4R in special circumstances: this demands context-specific flexibility in areas and populations where rifapentine is unavailable or contraindicated, in pregnant women and children, or in persons exposed to multidrug-/rifampicin-resistant TB who may require tailored options. National health authorities need to facilitate regulatory approvals, include drugs on essential medicines and procurement lists, and step up efforts to secure sustainable funding from both domestic and external sources. TPT should be embedded within routine ART services and included in the training syllabus for health workers, who need to know about appropriate regimen use, TB screening, and managing side-effects and drug-drug interactions with ARVs. Monitoring and evaluation systems should track regimen-specific initiation, adherence and outcomes to feed into programme decisions and improve coverage. Community engagement is essential to address stigma, promote TPT as a critical lifesaving intervention and gain adherence through peer support, digital tools and incentives. Tailored approaches are needed for special populations, including regimen choices for pregnant women and children, and expanded access to child-friendly formulations. **Table 5.2** summarizes various concerns and considerations related to implementation.

Table 5.2 Implementation considerations by programme area

Programme area	Implementation considerations
Regimen prioritization	• Prioritize 3HP as the preferred TPT regimen; guide transition as needed. • Maintain access to 6H/9H alternatives; guarantee availability of 1HP, 3RH, 4R 6Lfx for use in special circumstances.
Regulatory and financing	• Register rifapentine* and update national guidelines. • Secure sustainable financing from domestic and external sources.
Services integration	• Embed TPT provisions into ART services and maternal and child care. • Train health workers on TPT regimens, TB screening and management of side-effects and drug-drug interactions with ARVs.
Access and supply chain	• Add rifapentine to national essential medicines lists. • Ensure procurement and consistent supply of rifapentine, including FDC. • Facilitate national, regional and global mechanisms to assure reliable access to shorter regimens in countries*
Monitoring and evaluation	• Track TPT initiation, adherence and outcomes by regimen. • Use data to inform programme decisions and improve coverage.
Community engagement	• Address stigma issues and promote TPT as essential lifesaving intervention for people living with HIV along with ART. • Support counselling and adherence support through peer, digital and incentive-based approaches.
Special populations	• Offer choice of regimens for pregnant women and children. • Ensure availability of child-friendly formulations. • Secure options for key and vulnerable populations.

*In several high TB-burden LMIC countries, rifapentine is not registered, despite its inclusion in WHO's list of essential medicines and its approval by the US Food and Drug Administration (FDA); it still awaits registration with the European Medicine Agency (EMA).

Shorter TPT regimens, particularly 3HP, among people living with HIV are known to have high completion rates and favourable safety profiles compared to daily isoniazid for six months. Implementation studies in Uganda and South Africa have reported treatment completion rates exceeding 80% among PLHIV, highlighting the regimen's acceptability and feasibility within routine HIV care settings *(18,27,28)*. Some similar examples are summarized in **Table 5.3**.

Table 5.3 Examples of country implementation of 3HP as TPT in people living with HIV

Country	Implementing/ Supporting Entity	Description	Coverage/Results
South Africa	IMPAACT4TB	National scale-up of 3HP with focus on PLHIV; supported by IMPAACT4TB.	≥ 80% treatment completion; high patient and provider acceptability.
Uganda	CHAI, Unitaid	Integration of 3HP into routine HIV care; emphasis on health care worker training and drug supply.	Approximately 70% adherence; improved outcomes with 3HP compared to 6H.
India	National TB Elimination Programme (NTEP)	Pilot studies in high-burden districts; evaluating feasibility, adherence, and safety.	Pilot data shows high adherence and minimal adverse effects.
Brazil	Ministry of Health	National guideline inclusion of 3HP; integration within primary care and provider training.	Wide acceptance: early implementation showed high tolerability.

Pharmacokinetic studies indicate that co-administration of 3HP, dolutegravir and efavirenz is generally safe and there is no need to adjust the ARV dose; nevertheless, regular clinical monitoring during TPT should be provided *(29)*. Limited data on the use of 3HP during pregnancy provide preliminary reassurance about its safety, with studies showing no significant increase in adverse pregnancy outcomes compared to traditional regimens *(30)*. Some studies assessing the preferences of health care providers and patients have found a strong preference for 3HP over daily regimens such as 6H, 9H and even 1HP, due to its shorter duration, lower pill burden and less frequent dosing, all of which align better with routine HIV care workflows and reduce patient fatigue *(18,30,31)*.

5.1.6 Research gaps

Despite global advances in the care of HIV and tuberculosis (TB), significant research gaps hinder the optimal implementation of TPT among people living with HIV. These gaps have clinical, pharmacological, operational and sociobehavioural dimensions, and limit the effectiveness and equity of TPT programmes. Urgent research is needed to inform policy and improve outcomes for this high-risk population.

Pregnant women, children, adolescents, older adults and individuals with comorbidities remain underrepresented in TPT studies. For instance, limited data on the safety of shorter-course regimens such as 3HP in pregnant women with HIV constrains their inclusion in global and national policies *(32)*. The pharmacological interplay between TPT drugs – especially rifapentine – and antiretroviral drugs (ARV), notably dolutegravir-based regimens, is not well characterized *(9)*. A lack of predictive biomarkers and reliable TB exclusion diagnostics complicates treatment decisions, potentially leading to missed opportunities for prevention *(33,34)*. Effective models for integrating TPT into differentiated HIV service delivery are not well established. Research is also needed to understand how to support adherence and delivery at scale *(35,36)*. Data on the cost-effectiveness of TPT regimens in low- and middle-income countries are limited, and access to rifapentine remains constrained by regulatory and supply chain barriers *(37,38)*. TB-related stigma and disparities across gender, geography and marginalized populations inhibit TPT uptake and completion, and research is needed to guide stigma reduction and inclusive strategies *(39,40)*. The duration of TPT's protective effect is unclear, and the safety of repeat or booster regimens insufficiently studied. Surveillance systems to monitor drug resistance may require some strengthening *(1,41,42)*.

A summary of research gaps is presented in **Table 5.4**. Addressing these evidence gaps is essential to strengthen the role of TPT in ending TB among people living with HIV. Prioritizing inclusive research, developing supportive diagnostics and drug formulations, and overcoming implementation barriers will be key aspects in moving towards equitable and sustained health outcomes.

Table 5.4 Summary of research gaps and relevance

Focus area	Gap	Why relevant or significant
Pregnant and breastfeeding women	Limited safety and pharmacokinetic data for shorter-course TPT (3HP, 1HP).	Pregnant women with HIV are at increased TB risk but often excluded from trials.
Children and adolescents < 13 years old	Lack of evidence on safety, optimal rifapentine-based TPT dosing and long-term outcomes.	Young PLHIV have distinct pharmacological needs and age-related developmental factors.
Older adults and those with comorbidities	Insufficient safety data for high-risk comorbid populations.	Comorbidities may alter drug metabolism or increase adverse events.
Coformulated treatment options	Lack of optimized fixed-dose combinations based on ART and TPT drugs.	Simplified regimens could improve adherence and reduce pill burden.
Biomarkers to guide TPT use in PLHIV	Scarce evidence on biomarkers to predict persons most likely to benefit from TPT.	Biomarkers help avoid overtreatment and focus on those at greatest risk.
TB exclusion diagnostics	Diagnostics to safely rule out active TB before TPT initiation.	Would enable correct use of TPT and prevent drug resistance.
Integration with HIV care	Unclear which models are best suited to integrate TPT into differentiated HIV care services.	Integrated care can improve outreach and adherence; tailored implementation strategies needed.
Adherence and completion	Limited evidence on improving real-world adherence.	Non-completion undermines individual and public health impact.
Stigma and community perceptions	Impact of stigma on TPT uptake is poorly understood.	Stigma can block initiation or continuation of care.

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06

Plans for dissemination, adaptation, implementation and evaluation of the guideline

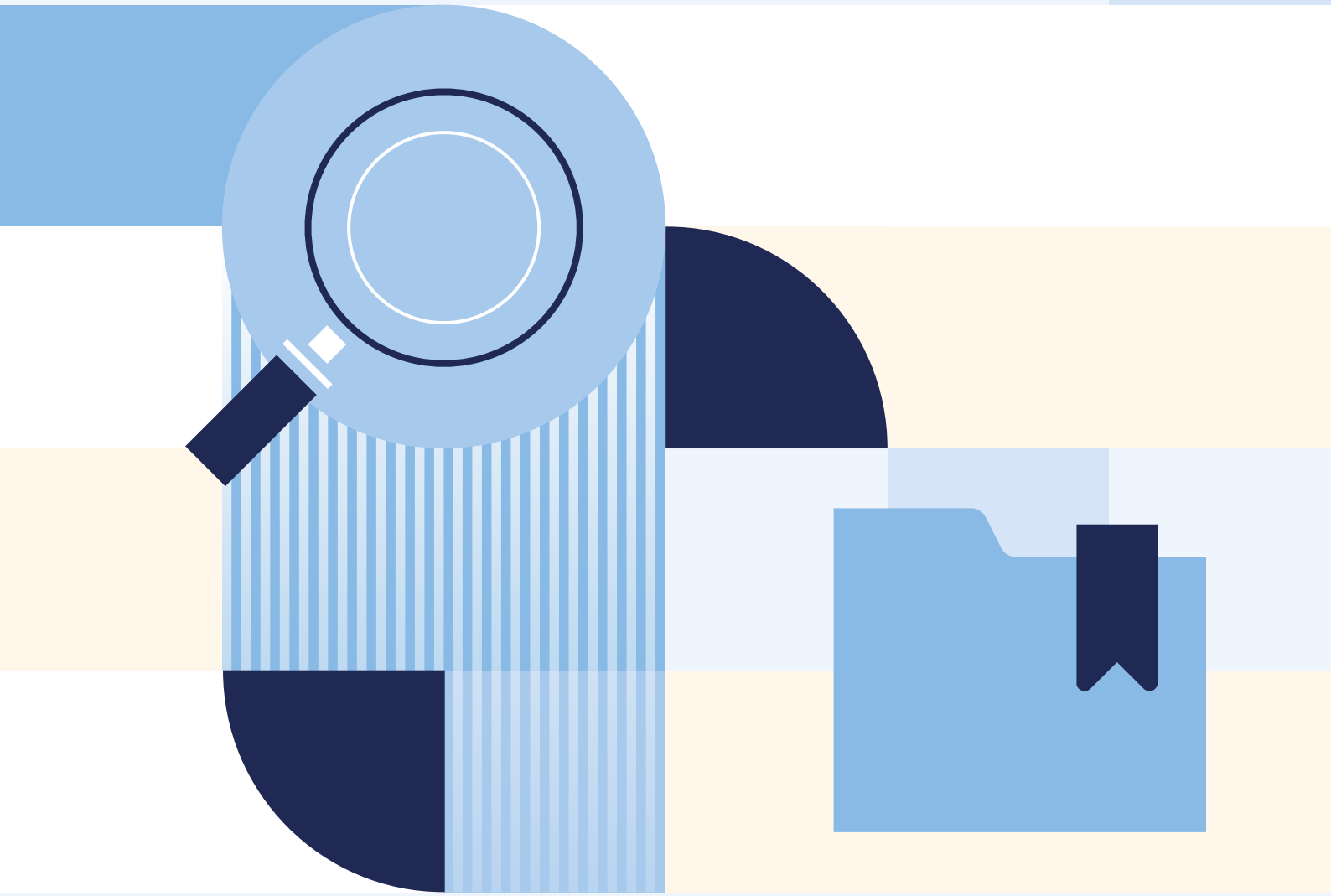
6. Plans for dissemination, adaptation, implementation and evaluation of the guideline

This guideline will be produced for dissemination as a web-based product and supported by peer-reviewed publication of the systematic reviews on which the recommendations are based. A policy brief and slide set will accompany publication of the guideline.

WHO will also incorporate this guideline into the next full update of its consolidated ARV guidelines planned for 2025/2026. WHO will closely monitor data on the use of oral and injectable dual regimens and regularly review emerging data. WHO will also monitor any emerging potential side-effects related to the use of CAB+RPV, DRV/r, TAF and other ARVs.

WHO will work closely with the Organization's regional and country offices, national health ministries, implementing partners and networks of people living with HIV and plan to disseminate, adapt and implement the new recommendations as rapidly as possible. Key steps in this procedure include presenting the recommendations at international conferences, holding workshops to support country adaptation, developing adaptation tools to assist countries in setting priorities, and ensuring briefings and joint planning with international and national implementing partners. The uptake and enactment of these recommendations in national guidelines will be assessed yearly from 2025.

Annexes



Annex 1. Process for developing the guideline

Methods for evidence synthesis

Key information sources

The WHO Guideline Steering Group formulated PICO (population, intervention, comparator and outcome) questions to guide the systematic reviews used in developing the guideline. The following PICO questions relevant to this guideline were identified.

- **PICO 1:** Should DRV/r be preferred over ATV/r and LPV/r in second-line regimens for adults, pregnant women and children?
- **PICO 2:** Should AZT replace tenofovir (TDF or TAF) or ABC in second-line NRTI backbones, or should tenofovir (TDF or TAF) or ABC be recycled regardless of NRTI resistance?
- **PICO 3:** Should TAF be preferred over TDF as the preferred option in the NRTI backbone for people living with HIV on ART?
- **PICO 4:** Should dual-therapy regimens be recommended as either a first-line or ART simplification strategy for people living with HIV?
- **PICO 5:** Which is the preferred ARV prophylaxis for HIV-exposed infants born to mothers living with HIV, on antiretroviral therapy and virally suppressed *("routine or low risk")*?
- **PICO 6a:** Which is the preferred combination of ARVs to prevent acquisition of HIV in infants at high risk of vertical transmission due to maternal viraemia identified during pregnancy or delivery *("high risk")*?
- **PICO 6b:** Which is the preferred combination of ARVs to prevent acquisition of HIV in breastfeeding infants at high risk of vertical transmission due to maternal viraemia identified during breastfeeding?
- **PICO 7:** Should breastfeeding be proposed and supported as an infant feeding choice for mothers living with HIV on ART in settings or in programmes where replacement feeding is routinely recommended?
- **PICO 8:** For women living with HIV and receiving ART, what kinds of enhanced monitoring, counselling and support should be provided to support their infant feeding decisions?
- **PICO 9:** For adults and adolescents living with HIV which should be the preferred shorter TB preventive treatment (TPT) regimen: less than or equal to 6 months?

A list of potential outcomes of interest for each question was circulated to all members of the Guideline Development Group, and members scored the importance on a scale of 1 (not important) to 9 (critical). The median score for each outcome was used to inform decision-making.

Systematic review teams developed protocols and conducted reviews in accordance with PRISMA *(1)* reporting items for systematic reviews and meta-analyses. Network meta-analyses were also used in some reviews to compare direct and indirect evidence on the use of some ARVs.

The detailed review of evidence includes ongoing or planned clinical trials, research studies, surveillance programmes, post-marketing surveillance including methodology, protocols and emerging results and periodic safety updates provided by drug regulatory authorities, research agencies, pregnancy registries or birth defect surveillance programmes.

Values and preferences

Data collection and analytical reports related to the values and preferences of people living with HIV were undertaken by a community network (GNP+). They conducted surveys and several qualitative focal group discussions with people living with HIV to explore their views on the use of ARVs, management of vertical HIV transmission and TB prevention. Information regarding values and preferences regarding these topics was presented to the Guideline Development Group and has been made available (Web Annex C).

Resource use and costs

Information on resource use, costs and cost-effectiveness was collected and cross-referenced from the literature and other WHO publications, including ongoing disease modelling work. Complementary information identified through programmatic data, information gathered from key informant interviews as well as available cost data of medications and other treatment interventions were also considered.

Feasibility

Information on feasibility was identified through the literature reviews, values and preferences survey/focal group discussions and key informant interviews with HIV programme managers and procurement officers.

Implementation considerations and research gaps

Knowledge gaps were identified through the systematic review process and complemented by several critical research gaps detected during the research landscape mapping exercise. The final guideline document will contain a summary of the identified knowledge gaps as identified through the evidence review process and based on suggestions from the Guideline Development Group.

Certainty of the evidence and the strength of the recommendations

The GRADE method was used to rate the certainty of the evidence and determine the strength of the recommendations *(2)*. The GRADE approach to developing recommendations, as adopted by WHO, defines the certainty of evidence as the extent to which one can be confident that the reported estimates of effect (desirable or undesirable) available from the evidence are close to the actual effects of interest. The strength of a recommendation reflects the degree of confidence of the Guideline Development Group that the desirable effects of the recommendation outweigh the undesirable effects. Desirable effects (potential benefits) may include beneficial health outcomes (such as reduced morbidity and mortality), reducing the burden on the individual and/or health services and potential cost savings. Undesirable effects (potential harm) include those affecting individuals, families, communities or health services. Additional burdens considered include the resource use and cost implications of implementing the recommendations and clinical outcomes (such as drug resistance and drug toxicity).

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

A strong recommendation (for or against) is one for which there is confidence that the desirable effects of adhering to the recommendation clearly outweigh the undesirable effects.

A conditional recommendation (for or against) is one for which the certainty of the evidence may be low or may apply only to specific groups or settings. The Guideline Development Group concludes that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects or are closely balanced, but is not confident about these trade-offs in all situations.

The certainty of the evidence, values and preferences of the end-users, feasibility, resource implications and due consideration of the potential benefits and harms contribute to determining the strength of a recommendation.

Guideline Development Group meeting

The Guideline Development Group met virtually in 10 sessions held between 18 and 27 February 2025. They reviewed evidence, values, acceptability, equity impact, resource use, costs, cost-effectiveness and feasibility. Evidence-to-decision tables were prepared according to the GRADE process and discussed with a facilitator. The group agreed on a 70% voting requirement for decisions, but consensus was reached on all recommendations. The group also discussed and listed the key implementation considerations and research gaps for each recommendation. Meeting minutes were recorded and summarized for later review.

Declarations of interest and biographies of Guideline Development Group members

All external contributors to the development of this guideline completed a WHO declaration of interests form. This included systematic reviewers and contributors to the supporting evidence as well as all members of the Guideline Development Group and External Review Group. In accordance with WHO's declaration of interests policy for experts, a brief biography of each Guideline Development Group member was published on the WHO HIV website with a description of the objective of the meeting[1]. No public comments or objections were received concerning any group members.

The technical officers in charge reviewed all electronic declarations of interests and confidentiality agreement forms completed by Guideline Development Group members.

Every effort was made to ensure that representation within the Guideline Development Group minimized any conflicts of interest. A management plan for each declared conflict was previously agreed. All declared interests and management strategies were discussed with the co-chairs and methodologist before the Guideline Development Group meeting.

The following Guideline Development Group members declared no conflict of interest: Elaine Abrams, Amgad Ali Alzahaby, Alexandra Calmy, Polly Clayden, Aleny Couto, Rossana Ditangco, Kelly Dooley, Nagalingeswaran Kumarasamy, Thuy Lee, Shain Lockman, Imelda Mahaka, Othoman Mellouk, Lindwe Mvusi, Lloyd Mulenga, and Nini Tun. The following members declared research funding, speaking events, travel or advisory roles: Moherndran Archery, Pedro Cahn, Lameck Chinula, Charles Flexner, Thanyawee Puthanakit, Beatriz Grinsztejn, Graeme Meintjes, Lynne Mofenson, Victor Musiime, Anton Pozniak, Anna Turkova, and Francois Venter. The WHO secretariat, along with co-chairs and methodologist, reviewed these declarations and found no significant financial or scientific conflicts, allowing full participation of all members.

The summary analysis of the conflicts of interest forms was shared with the Guideline Development Group at the start of the meeting, with participation closely monitored by the responsible technical officers and GRADE methodologist.

All declaration of interests forms are available on electronic file at the WHO HHS Department and will be maintained for at least 10 years.

External Review Group

Each member of the External Review Group was asked to complete and sign a declaration of interests and confidentiality agreement form. WHO technical officers in charge reviewed these forms to determine whether there were any conflicts of interest. Comments from the External Review Group were interpreted in the light of any apparent conflicts of interest.

The following External Review Group members declared no conflict of interest: Serge Eholie, Antonio Flores, Catia Marzolini, and Barath Rewari. The following members declared research funding, speaking events or advisory roles: Roy Gulick, Diane Havlir, Mariana Iaconno, Valeriane Le Roy and Karin Laine. The WHO secretariat, along with co-chairs and methodologist, reviewed these declarations and found no significant financial or scientific conflicts, allowing full participation of all members.

All declaration of interests forms are available on electronic file at the WHO HHS Department and will be maintained for at least 10 years.

Peer review

A draft of the guideline was circulated for review to members of the Guideline Development Group and the External Review Group. WHO staff reviewed the comments and incorporated them into the final document with due consideration of any conflicts of interest. Comments were interpreted in the light of any conflicts of interest declared. Any conflicting or controversial comments were discussed with the WHO Guideline Steering Group. Disagreements were resolved by consensus within the WHO Guideline Steering Group.

[1] https://www.who.int/news/item/05-02-2025-who-announces-the-development-of-updated-recommendations-on-antiretroviral-therapy--management-of-vertical-hiv-transmission-and-tb-prevention-in-people-living-with-hiv

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Global HIV, Hepatitis and Sexually Transmitted Infections Programmes

World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland

www.who.int