World Health Organization

SUPPLEMENT

GUIDELINES

ON POST-EXPOSURE PROPHYLAXIS FOR HIV AND THE USE OF CO-TRIMOXAZOLE PROPHYLAXIS FOR HIV-RELATED INFECTIONS AMONG ADULTS, ADOLESCENTS AND CHILDREN: RECOMMENDATIONS FOR A PUBLIC HEALTH APPROACH

DECEMBER 2014 SUPPLEMENT TO THE 2013 CONSOLIDATED GUIDELINES ON THE USE OF ANTIRETROVIRAL DRUGS FOR TREATING AND PREVENTING HIV INFECTION

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ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
ART	antiretroviral therapy
ARV	antiretroviral
ATV/r	atazanavir/ritonavir
AZT	zidovudine
CI	confidence interval
DRV/r	darunavir/ritonavir
EFV	efavirenz
FTC	emtricitabine
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
ILO	International Labour Organization
LPV/r	lopinavir/ritonavir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
OR	odds ratio
PI	protease inhibitor
PICO	population, intervention, comparison and outcomes
RAL	raltegravir
RR	relative risk
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development

DEFINITIONS

GENERAL

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

HIV-1 is responsible for the vast majority of HIV infections globally. Within these guidelines, HIV refers to both HIV-1 and HIV-2 unless otherwise specified.

AGE GROUPS AND POPULATIONS

The following definitions for adults, adolescents, children and infants are used to ensure consistency within these consolidated guidelines, as well as with other WHO guidelines. It is recognized that other agencies may use different definitions.

An **adult** is a person older than 19 years of age unless national law defines a person as being an adult at an earlier age.

An **adolescent** is a person aged 10 to 19 years inclusive.

A **child** is a person 19 years or younger unless national law defines a person to be an adult at an earlier age. However, in these guidelines when a person falls into the 10 to 19 age category they are referred to as an adolescent (see adolescent definition).

An **infant** is a child younger than one year of age.

HEALTH CARE SERVICES

Continuum of HIV care refers to a comprehensive package of HIV prevention, diagnostic, treatment and support services provided for people living with HIV and their families ranging across: initial HIV diagnosis and linkage to care; management of opportunistic infections and other comorbid conditions; initiating, maintaining and monitoring ART; switching to third-line ART; and palliative care.

A public health approach addresses the health needs of a population or the collective health status of the people rather than just individuals. A public health approach involves a collaborative effort by all parts of the health sector, working to ensure the well-being of society through comprehensive prevention, treatment, care and support. For HIV, this involves: simplified limited formularies; large-scale use of fixed-dose combinations for first-line treatment for adults and children; care and drugs given free at the point of service delivery; decentralization; and integration of services, including task shifting and simplified clinical and toxicity monitoring.

HIV TESTING AND PREVENTION

Voluntary counselling and testing (also referred to as client-initiated testing and counselling) describes a process initiated by an individual who wants to learn his or her HIV status. Since there are now many different community approaches to providing HIV testing and counselling and people often have mixed motivations for seeking testing (both recommended by a provider and sought by a client), WHO prefers to use the term HIV testing and counselling. All forms of HIV testing and counselling should be voluntary and adhere to the five C's: consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services. Quality assurance of both testing and counselling is essential in all approaches to HIV testing and counselling.

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

ART (ANTIRETROVIRAL THERAPY)

ARV (antiretroviral) drugs refer to the medicines themselves and not to their use.

ART refers to the use of a combination of three or more ARV drugs to achieve viral suppression. This generally refers to lifelong treatment. Synonyms are combination ART and highly active ART.

ART for prevention is used to describe the HIV prevention benefits of ART.

Eligible for ART refers to people living with HIV for whom ART is indicated according to the definitions of clinical and immunological eligibility in WHO treatment guidelines. The term is often used interchangeably with "needing treatment", although this implies an immediate risk or an obligation to initiate treatment.

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Post-exposure prophylaxis for HIV

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The use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children

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EXECUTIVE SUMMARY

In 2013, WHO produced the first consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, which were structured along the continuum of care. Since that time, WHO has committed to providing regular and predictable updates to these guidelines and to supplement these guidelines with new recommendations as new evidence becomes available. In March 2014, WHO released the first supplement to the 2013 antiretroviral (ARV) guidelines, which compiled a number of technical updates reflecting guidance on how best to implement the 2013 ARV guidelines.

In this second supplement to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, recommendations from two guideline development processes are included:

- post-exposure prophylaxis for HIV;
- the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children.

These guidelines provide new recommendations and updates to previous recommendations outlined in Chapter 5 (ARV drugs for HIV prevention) and Chapter 8 (Managing common coinfections and comorbidities) of the 2013 consolidated ARV guidelines, and following the similar structure of the 2013 ARV guidelines, these recommendations are organized along the continuum of care. These guidelines reflect important advances in the use of ARV drugs to prevent HIV with more simplified approaches to post-exposure prophylaxis and simplifying the indications on the use of co-trimoxazole to prevent opportunistic infections, bacterial infections and malaria. Consistent with previous WHO guidelines, these guidelines are based on a public health approach that considers feasibility and effectiveness across a variety of settings. The key principles of availability, affordability, acceptability, accessibility and quality have been considered in producing these recommendations.

The primary audience for these guidelines is policy-makers and programme managers of HIV and disease control programmes. Health facilities and teaching institutions are also expected to use the guidelines to set up and maintain care services. In addition, the guidelines will be of interest to health professionals who are responsible for providing care to children, adolescents and adults in settings with HIV, primarily in low- and middle-income countries.

This first section of this supplement addresses post-exposure prophylaxis for HIV and provides updated recommendations on the use of ARV drugs as post-exposure prophylaxis to prevent HIV infection among individuals exposed to a potential source of HIV. The objective of this section is to provide updated evidence-informed recommendations based on systematic reviews.

In contrast to the 2007 WHO guidelines for post-exposure prophylaxis, these guidelines consider all types of exposure and provide recommendations for all populations. In doing so, no distinction between occupational and non-occupational settings has been made, with the aim of simplifying guidance for post-exposure prophylaxis prescribing and improving access; the same drug regimen should be prescribed irrespective of exposure source. Recommendations for preferred regimens, simplifying prescribing approaches and supporting adherence are also provided. Practical guidance is also given on assessing eligibility for post-exposure prophylaxis, follow-up testing and linkage to treatment and prevention services and specific considerations for the support and care package required for different categories of exposure with reference to existing guidelines and resources.

The second section of this supplement provides recommendations for the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children. Since the early years of HIV pandemic, co-trimoxazole prophylaxis has been considered as a feasible, well tolerated and cost-effective intervention to prevent opportunistic infections and reduce HIV-related morbidity and mortality among people living with HIV. Co-trimoxazole prevents and treats a variety of bacterial, fungal and protozoan infections. In 2006, WHO guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults were issued. Those guidelines recommended co-trimoxazole prophylaxis to be implemented as an integral component of the HIV care package and a key element of the pre-antiretroviral therapy (pre-ART) care in low- and middle-income countries. The focus then was on people with advanced and severe disease with limited access to ART. Recently, new evidence has emerged that, with effective scaling up of ART, co-trimoxazole prophylaxis has a broader benefit beyond preventing *Pneumocystis jirovecii* pneumonia and reducing HIV-associated mortality among people with low CD4 counts. Specifically, the value of using co-trimoxazole prophylaxis to prevent malaria and severe bacterial infections in adults and children with HIV was reviewed when developing the systematic evidence to inform this new guidance. The progressive movement towards earlier initiation of ART warranted an update to existing WHO guidelines on co-trimoxazole prophylaxis.

These updated recommendations have expanded the use of co-trimoxazole for all populations, at any CD4 threshold and for a longer duration, for preventing HIV-related opportunistic infections but also for the preventive benefit of reducing mortality and morbidity from severe bacterial and malaria infections among adults, adolescents and children living in resource-limited settings.

These guidelines are an important addition to the 2013 ARV guidelines and support improved ARV-based prevention (post-exposure prophylaxis for HIV) and the prevention of opportunistic infections with major public health impact on mortality and morbidity; implementation of these guidelines is one step in the movement towards realizing the United Nations goal of ending AIDS by 2030.

SUMMARY OF NEW RECOMMENDATIONS

The following table summarizes the new and updated WHO recommendations presented in this supplement.

Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children		
Recommendation	**Strength**	**Quality of the evidence**
Post-exposure prophylaxis for HIV		
Number of antiretroviral drugs		
An HIV post-exposure prophylaxis regimen with two antiretroviral drugs is effective, but three drugs are preferred.	Conditional	Low
Preferred antiretroviral regimen for adults and adolescents[a]		
TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis among adults and adolescents.	Strong	Low to moderate
LPV/r or ATV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis among adults and adolescents. Where available, RAL, DRV/r or EFV can be considered as alternative options.	Conditional	Very low
Preferred antiretroviral regimen for children ≤10 years old[b]		
AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis among children 10 years and younger. ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens.	Strong	Low
LPV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis among children younger than 10 years. An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV and NVP.	Conditional	Very low
Prescribing frequency		
A 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment.	Strong	Very low
Adherence support		
Enhanced adherence counselling is suggested for all individuals initiating HIV post-exposure prophylaxis.	Conditional	Moderate
The use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children		
Recommendation	**Strength**	**Quality of the evidence**
Adults (including pregnant women)[c]		
Co-trimoxazole prophylaxis is recommended for severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or for a CD4 count ≤350 cells/mm^3. • In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.	Strong Strong	Moderate Moderate

Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children		
Recommendation	**Strength**	**Quality of the evidence**
Co-trimoxazole prophylaxis may be discontinued in adults (including pregnant women) with HIV infection who are clinically stable on antiretroviral therapy, with evidence of immune recovery and viral suppression.	Conditional	Low
• In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage.	Conditional	Moderate
Infants, children and adolescents[d]		
Co-trimoxazole prophylaxis is recommended for infants, children, and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage and to children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with CD4 ≤350 cells/mm^3.	Strong	High
• In settings with a high prevalence of malaria and/or severe bacterial infections, co-trimoxazole prophylaxis should be continued until adulthood irrespective of antiretroviral therapy provision.	Conditional	Moderate
• In settings with low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virally suppressed on antiretroviral therapy for at least 6 months and CD4 >350 cells/mm^3.	Strong	Very low
HIV-exposed infants		
Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from 4–6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding.	Strong	Very low
LPV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis among children younger than 10 years. An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV and NVP.	Conditional	Very low
HIV and TB coinfection		
Routine co-trimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts.	Strong	High

[a] Adult and Adolescent ARVdrug dosages for use in PEP	
Generic name	**Dose**
Tenofovir (TDF)	300 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily or 800 mg/200 mg once dailya
Atazanavir/ritonavir (ATV/r)	300 mg +100 mg once daily
Raltegravir (RAL)	400 mg twice daily
Darunavir + ritonavir (DRV/r)	800 mg +100 mg once daily or 600 mg +100 mg twice daily
Efavirenz (EFV)	600 mg once daily

[b] Simplified dosing of child-friendly fixed-dose solid formulations of recommended preferred ARV drugs for post-exposure prophylaxis of HIV for twice-daily dosing among children

Drug	Strength of tablets (mg)	Number of tablets by weight band morning (AM) and evening (PM)										Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg			25.0–34.9kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300/150	1	1

Simplified dosing of child-friendly solid and oral liquid formulations of recommended preferred ARV drugs for post-exposure prophylaxis of HIV for twice-daily dosing among children

Drug	Strength of tablets (mg) or oral liquid (mg/ml)	Number of tablets by weight band, morning (AM) and evening (PM)										Strength of adult tablet (mg)	Number of tablets by weight band	
		3.0–5.9 kg		6.0–9.9 kg		10.0–13.9 kg		14.0–19.9 kg		20.0–24.9 kg			25.0–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations														
3TC	Tablet (dispersible) 30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	150	1	1
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300	1	1
LPV/r	Tablet (heat stable) 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	100/25	3	3
Liquid formulations														
AZT	10 mg/ml	6 ml	6 ml	9 ml	9 ml	12 ml	12 ml	–	–	–	–	–	–	–
3TC	10 mg/ml	3 ml	3 ml	4 ml	4 ml	6 ml	6 ml	–	–	–	–	–	–	–
LPV/r*	80/20 mg/ml	1 ml	1 ml	1.5 ml	1.5 ml	2 ml	2 ml	2.5 ml	2.5 ml	3 ml	3 ml	–	–	–

*LPV/r syrup should not be used for premature babies or infants younger than 2 weeks of age. NVP should be used instead at the following dose: 5 ml twice daily (3.0–5.9 kg), 8 ml twice daily (6.0–9.9 kg) and 10 ml twice daily (10.0–13.9 kg) if syrup is available; 1 tablet twice daily (3.0–5.9 kg), 1.5 tablets twice daily (6.0–9.9 kg) and 2 tablets twice daily (10.0–13.9 kg) if dispersible 50-mg tablets are available.

[c] Co-trimoxazole dosing for adults and adolescents: the recommended dose of co-trimoxazole is 960 mg daily (800 mg sulfamethoxazole + 160 mg trimethoprim, either as a 960-mg double-strength tablet or two 480-mg single-strength tablets)

[d] Simplified dosing of co-trimoxazole prophylaxis for children

Drug	Strength of tablet or oral liquid (mg or mg/5 ml)	Number of tablets or ml by weight band once daily					
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg	25.0–34.9 kg
Co-trimoxazole	Suspension 200/40 mg per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	1

1. INTRODUCTION

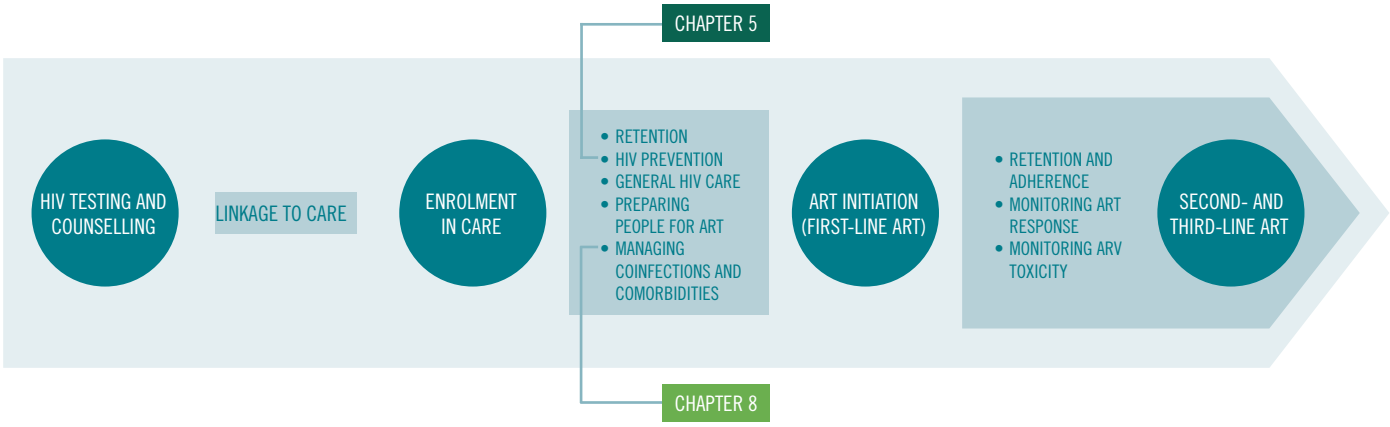
1.1 Background and context

These guidelines provide updated and new recommendations on the use of antiretroviral (ARV) drugs and serve as the second supplement to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)*. The focus of these guidelines is to prevent HIV infection by simplifying and expanding post-exposure prophylaxis for HIV and the prophylaxis of opportunistic infections, with the expanded use of co-trimoxazole to prevention opportunistic infections along with severe bacterial infections and malaria.

1.2 Organization of the guidelines

These guidelines have adopted a similar format and structure as the 2013 WHO ARV guidelines *(1)*; recommendations are presented across the continuum of care for all populations and serve as updates to the current Chapters 5 and 8 of the 2013 WHO ARV guidelines (Fig. 1.1).

Figure 1.1 ARV guidelines along the continuum of care



Source: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (1).

The recommendations in the 2013 ARV guidelines address key aspects of using ARV drugs for HIV treatment and prevention for all age groups and populations along the continuum of care, from HIV-related diagnosis to care and treatment.

Chapter 5 of the 2013 WHO ARV guidelines *(1)* summarizes HIV testing and counselling approaches, with links to existing WHO guidance. In addition, it summarizes approaches to using ARV drugs for preventing HIV transmission (pre-exposure prophylaxis and post-exposure prophylaxis of HIV and ARV drugs for prevention in serodiscordant couples) within the context of comprehensive combination HIV prevention, with links to existing WHO guidance. Previous guidelines on post-exposure prophylaxis were published in 2007 *(2)*.

Chapter 8 of the 2013 WHO ARV guidelines *(1)* includes a summary of approaches to preventing and managing common HIV-related opportunistic infections, other coinfections and other comorbidities, with links to existing WHO guidance. Previous guidelines on the use of co-trimoxazole were published in 2006, and new evidence called for an update *(3)*.

1.3 Rationale for consolidating the guidelines in this supplement

These guidelines offer the following anticipated benefits.

- Guidance on using ARV drugs is presented within the context of the continuum of HIV-related prevention, treatment and care.
- The guidelines address the use of ARV drugs for all age groups and populations.
- New and existing guidance is harmonized.
- Consolidated recommendations help to facilitate linkage and promote consistency of approaches across the various settings in which ARV drugs and related services may be provided.
- Updates will be more timely and comprehensive. Consolidated guidelines enable the key clinical, operational and programmatic implications of new science and emerging practice in the use of ARV drugs to be comprehensively reviewed every 2 years and updates such as this supplement to be shared as needed between formal biennial updates.

1.4 Objectives

1.4.1 Post-exposure prophylaxis for HIV

This section provides evidence-informed recommendations on providing post-exposure prophylaxis for all populations (adults, adolescents and children), for all types of potential exposure (occupational and non-occupational) in all settings.

Specific recommendations include:

- preferred drug choices for adults and adolescents;
- preferred drug choices for children ≤10 years old; and
- prescription methods and adherence support.

In addition, practical guidance is given on assessing eligibility for post-exposure prophylaxis and providing follow-up testing and linkage to treatment and prevention services. The scope of the guideline is limited to drug regimen and prescribing practices. References to relevant guidelines from WHO and other sources are provided to support best practice considerations.

1.4.2 The use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children

This section has reviewed the most recent evidence on the use of co-trimoxazole for preventing opportunistic and bacterial infections and malaria among people living with HIV and provides updated recommendations on when to start and when to stop co-trimoxazole prophylaxis.

Specific recommendations include:

- when to start for adults (including pregnant women) and children (including adolescents);
- when to stop for adults (including pregnant women) and children (including adolescents);
- when to stop for HIV-exposed uninfected infants;
- the safety of co-trimoxazole in pregnancy; and
- co-trimoxazole dosage for prophylaxis in adults.

1.5 Target audience

These guidelines are aimed at national HIV programme managers and policy-makers involved in implementing HIV programmes and providing services and will also be of interest to the following individuals and groups:

- health workers involved in providing ARV drugs, post-exposure prophylaxis, and co-trimoxazole in low- and middle-income countries;
- agencies involved in procuring drugs for ART, post-exposure prophylaxis and co-trimoxazole;
- developers of guidelines for health services involved in the provision of ARV drugs, post-exposure prophylaxis and co-trimoxazole (such as HIV programmes and emergency services);
- developers of guidelines for relevant professional associations;
- partners supporting the implementation of HIV care and treatment services and organizations providing technical and financial support to HIV care and treatment programmes in low- and middle–income countries; and
- organizations working with survivors of sexual assault and key populations (particularly for HIV post-exposure prophylaxis recommendations).

1.6 Scope and components

The recommendations have been developed with a focus on settings with limited health system capacity and resources and a high burden of HIV. These guidelines address post-exposure prophylaxis options to prevent HIV infection and the use of co-trimoxazole prophylaxis among people with HIV-related infections.

1.6.1 Introductory sections

Section 1 describes the background context, rationale and objectives of the guidelines and the target audience. Section 2 outlines the methods and processes for developing the guidelines, and Section 3 presents the guiding principles.

1.6.2 Clinical and operational guidance

Sections 4 and 5 present the key recommendations, rationale and supporting evidence for post-exposure prophylaxis of HIV and the use of co-trimoxazole for preventing opportunistic and bacterial infections and malaria. These two sections further expand and simplify the use of these drugs across populations and across settings.

2. METHODS

2.1 General considerations

2.1.1 Evidence assessment

Under the WHO guideline development process, the guideline development group formulates the recommendations guided by the quality of available evidence. Other factors such as values and preferences, costs and feasibility are also considered in determining the strength of the recommendation.

2.1.2 How to interpret the quality of evidence

The GRADE approach to recommendation development, which WHO has adopted, defines the quality 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 GRADE approach specifies four levels of quality of evidence *(1–5)* (Table 2.1).

Table 2.1 Significance of the four GRADE levels of evidence

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

2.1.3 Determining the strength of a recommendation

The strength of a recommendation reflects the degree of confidence of the guidelines group that the desirable effects of the recommendation outweigh the undesirable effects based on the quality of the evidence. Desirable effects (potential benefits) may include beneficial health outcomes (such as reduced incidence of HIV and reduced morbidity and mortality); reduction of burden on the individual and/or health services; and potential cost savings for the individual, communities, programme and/or health system. Undesirable effects (potential harms) include those affecting individuals, families, communities or health services. Harms that may be considered include the resource use and cost implications of implementing the recommendations that programmes, care providers or patients would have to bear; adverse clinical outcomes (such as drug resistance and drug toxicity); and legal ramifications where certain practices are criminalized.

The strength of a recommendation can be either strong or conditional (Table 2.2).

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

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

If implemented, a conditional recommendation should be monitored closely and evaluated rigorously. Further research will be required to address the uncertainties and is likely to provide new evidence that may change the calculation of the balance of trade-offs.

The values and preferences of the end users, feasibility, cost as well as consideration of potential benefits and harms contribute to determining the strength of a recommendation.

Table 2.2 Domains considered when assessing the strength of recommendations

Domain	Rationale
Benefits and risks	When a new recommendation is developed, desirable effects (benefits) need to be weighed against undesirable effects (risks), considering any previous recommendation or another alternative. The larger the gap or gradient in favour of the benefits over the risks, the more likely that a strong recommendation will be made.
Values and preferences (acceptability)	If the recommendation is likely to be widely accepted or valued highly, it is likely that a strong recommendation will be made. If there is a great deal of variability or strong reasons that the recommended course of action is unlikely to be accepted, it is more likely that a conditional recommendation will be made.
Costs and financial implications	Lower costs (monetary, infrastructure, equipment or human resources) or greater cost–effectiveness are more likely to support a strong recommendation.
Feasibility	If an intervention is achievable in a setting where the greatest impact is expected, a strong recommendation is appropriate.

2.2 Post-exposure prophylaxis for HIV

2.2.1 Information sources

2.2.1.1 Evidence reviews

Systematic reviews were conducted on key topics to inform the recommendations:

- adherence to HIV post-exposure prophylaxis;
- prescription type for post-exposure prophylaxis (starter pack versus 28-day prescription);
- tolerability of TDF + 3TC (or FTC) in HIV-negative individuals;
- tolerability of LPV versus ATV in HIV-positive individuals;
- tolerability of EFV in HIV-positive individuals; and
- choice of ARV drug for HIV post-exposure prophylaxis for children (including safety and efficacy data from antiretroviral therapy for HIV-positive children).

For all systematic reviews, a predefined protocol was developed and multiple databases were searched (Medline via PubMed, EMBASE, the Cochrane Database of Systematic Reviews, Lilacs, Conferences of the International AIDS Society and the Conference on Retroviruses and Opportunistic Infections) with no geographical or language restrictions. Study selection and data extraction were performed in duplicate and the risk of bias assessed using established methods for randomized trials and observational studies. Measures of effect were pooled using random effects meta-analysis where appropriate. Evidence summaries using the GRADE assessment were compiled for each PICO (population, intervention, comparison and outcomes) question (Annex 1).

2.2.1.2 Evidence reviews

- E-survey of prescribers and health-care workers
  An electronic survey was conducted of health-care workers prescribing post-exposure prophylaxis for adults, adolescents and children to ascertain preference on drug choice, prescription methods and adherence support. A subsurvey was conducted on health-care workers with experience in taking post-exposure prophylaxis to inform preferences.

- Key populations
  Data from interviews with key populations gathered for the development of WHO guidelines on treatment of HIV in key populations were reviewed and summarized. Focus group discussions were held with female sex workers in Ghana in conjunction with FHI 360 and the Human Rights and Advocacy Centre in Ghana.

- General populations
  The literature on the barriers to prescription and completion of post-exposure prophylaxis was reviewed.

2.2.1.3 Feasibility

To compile quantitative data on drug choice, drug costing and availability data from the Global Price Reporting Mechanism database and WHO drug resistance survey data were extracted and evaluated for the drugs of interest.

2.2.1.4 Declarations of interests

All experts were requested to complete a declaration of interests form, and the responsible officer reviewed the responses. No member of the post-exposure prophylaxis Guideline Development Group or External Review Group declared any conflict of interest.

2.2.2 Process of formulating recommendations

All Guideline Development Group members approved evidence review questions and methods to support questions in advance of the meeting. Systematic reviews and evidence profiles were prepared and made available before the Guideline Development Group meeting and presented at the meeting. Evidence was supplemented by values and preferences, feasibility and cost data. The Guideline Development Group members rated the importance of outcomes before the meeting.

Proposed recommendations were considered using the evidence-to-decision framework facilitated by the methodologist. Guideline Development Group members reached consensus on recommendations and practical guidance. Where a vote was necessary, the group agreed that a two thirds majority was required to approve a recommendation.

2.3 The use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children

2.3.1 Information sources: evidence reviews

Systematic reviews were conducted on the following topics:

- co-trimoxazole use (when to start for adults, pregnant women, adolescents and children);
- when to stop for adults, pregnant women, adolescents and children;
- when to stop for HIV-exposed uninfected infants;
- the safety of co-trimoxazole in pregnancy; and
- co-trimoxazole dosage for prophylaxis among adults and children.

The systematic reviews included developing search protocols and reviewing the available scientific evidence. A standardized GRADE evidence table was used to present quantitative summaries of the evidence and the assessment of its quality for each question by outcome (Annex 2).

2.3.2 Process of formulating recommendations

The Guideline Development Group participants met during three working days to achieve the objectives.

The GRADE method was used to rate the quality of evidence and the strength of the recommendations (see above). At the meeting, decisions were intended to be made by consensus. Comments from the Guideline Development Group and the steering group were recorded and summarized and changes were incorporated before finalizing the recommendations.

When opposing views were offered, resolution was sought through discussion. Based on the quality of the evidence and the risk–benefit analysis that was agreed on, the Guideline Development Group discussed and decided on whether to make a strong recommendation, a conditional recommendation or no recommendation for each question. If there was no consensus on a proposed recommendation, a decision was made by majority vote.

2.3.3 Declaration of interests

All experts were requested to complete a declaration of interests form, and the responsible officer reviewed the responses. No member of the co-trimoxazole Guideline Development Group or External Review Group declared any conflict of interest.

3. GUIDING PRINCIPLES

3.1 Public health approach

These guidelines are based on the public health approach to delivering HIV services in accordance with the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection *(1)*. This approach seeks to ensure the widest possible access to high-quality services at the population level, aiming for a balance between the best proven standard of care and feasibility.

Consistent with this approach, individuals should be offered the standardized and simplified HIV post-exposure prophylaxis and the expanded and simplified use of co-trimoxazole to prevent HIV-related opportunistic infections as well as severe bacterial infections and malaria where indicated. For post-exposure prophylaxis, if the exposure constitutes a significant risk of transmission, the same drug regimen should be prescribed irrespective of the exposure source.

3.2 Promoting human rights and health equity

In the context of preventing infection (post-exposure prophylaxis) and preventing HIV-related opportunistic infections, key human rights obligations are to ensure the right to the highest attainable standard of health, to protect against violence and its consequences and to protect rights to privacy and confidentiality. A balance should be maintained between protecting population health and protecting individual human rights.

Eligibility for post-exposure prophylaxis and co-trimoxazole prophylaxis to prevent HIV-related infections should be based on the principles of equity and non-discrimination. For example, personal information relating to post-exposure prophylaxis provision or the use of co-trimoxazole to prevent HIV-related infections and to HIV testing should be confidential, and all interventions should follow the principles of informed consent followed for any other health care procedure. If the individual has limited or no capacity to consent, guidance should follow the principles of care as defined by national guidelines.

Post-exposure prophylaxis drugs and co-trimoxazole should be offered free of charge to everyone who meets eligibility criteria.

3.3 Implementation based on local context

National HIV programmes are strongly urged to provide post-exposure prophylaxis and co-trimoxazole prophylaxis in their overall national HIV strategic plan and to incorporate this guidance in their clinical guidelines. The local context, epidemiology, availability of resources and capacity of the health system should inform the implementation of the recommendations in these guidelines.

4. POST-EXPOSURE PROPHYLAXIS FOR HIV

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 5 – Clinical guidelines across the continuum of care: HIV diagnosis and ARV drugs for HIV prevention

4.1 New recommendations on post-exposure prophylaxis for HIV

4.1.1 Background

ARV drugs have been prescribed for post-exposure prophylaxis following occupational exposure to HIV for health workers since the early 1990s. During the past two decades, the provision of HIV post-exposure prophylaxis has been extended to non-occupational exposures, including unprotected sexual exposure, injecting drug use and exposure following sexual assault.

Previous guidelines issued by WHO together with the International Labour Organization (ILO) in 2007 *(1)* were based on expert opinion and focused on HIV post-exposure prophylaxis for adults following occupational exposure and sexual assault. The guidelines recommended providing a two- or three-drug post-exposure prophylaxis regimen following risk assessment of the exposure and the potential background drug resistance at the population level. ARV drug recommendations for post-exposure prophylaxis followed WHO guidelines for ART at that time *(2)*, giving preference to zidovudine (AZT) and lamivudine (3TC).

Since 2007, recommendations on the use of key antiretroviral drugs for preventing and treating HIV have changed. Some of the drugs listed as alternative drugs for post-exposure prophylaxis in 2007 (stavudine and saquinavir) are now no longer recommended for ART. The latest WHO guidelines for ART, issued in 2013 *(3)*, give preference to tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine (FTC) as a backbone for first-line treatment for adults and adolescents; harmonization of ART regimens for adults and children is recommended whenever possible.

This guideline provides updated recommendations for post-exposure prophylaxis regimens and prescribing practices. WHO aims to harmonize to the extent possible the ARV drug recommendations for post-exposure prophylaxis with current recommendations for the treatment of HIV infection. Recognizing the need to improve uptake and completion rates for post-exposure prophylaxis, this guideline emphasizes simplification and does not differentiate between exposure sources but rather provides recommendations across all exposures. Recommendations for simplifying prescribing approaches and supporting adherence are also provided.

4.1.2 Rationale for HIV post-exposure prophylaxis

Evidence supporting the use of ARV drugs for post-exposure prophylaxis comes from animal studies *(4)* and a single case-control study in health care workers *(5)* that demonstrated that ARV drugs could prevent the establishment of chronic HIV infection if administered within a short time following exposure. Systematic reviews of the effectiveness of post-exposure prophylaxis suggest that the use of ARV drugs following occupational and non-occupational exposure reduces the risk of acquiring HIV infection when administered as post-exposure prophylaxis and is likely to be cost-effective in high-risk groups *(6,7)*. The efficacy of ARV drugs in preventing HIV infection following exposure is further supported by the effectiveness of ARV drugs in preventing the mother-to-child transmission of HIV *(8)* and, more recently, pre-exposure prophylaxis *(9)*.

As with any prevention intervention, effectiveness depends critically on high levels of adherence and completion of the prescribed course; however, reported completion rates are currently suboptimal for post-exposure prophylaxis in most settings *(10,11)*. Other factors that may influence post-exposure prophylaxis effectiveness include the timing of initiation, level of exposure risk and possible drug resistance. Given these considerations, post-exposure prophylaxis may never be considered 100% effective, and post-exposure prophylaxis should form part of a wider strategy for avoiding acquiring HIV infection and other bloodborne viruses, including hepatitis B virus (HBV) and hepatitis C virus (HCV).

4.1.3 Objectives

This guideline provides evidence-informed recommendations on providing post-exposure prophylaxis for all populations (adults, adolescents and children), for all potential types of exposure (occupational and non-occupational) in all settings.

Specific recommendations include:

- preferred drug choices for adults and adolescents;
- preferred drug choices for children ≤10 years; and
- prescription methods and adherence support.

In addition, practical guidance is given on assessing eligibility for post-exposure prophylaxis and providing follow-up testing and linkage to treatment and prevention services.

The scope of the guideline is limited to drug regimen and prescribing practices. References to relevant guidelines from WHO and other sources are provided to support best practice considerations.

4.1.3.1 Clinical management of HIV post-exposure prophylaxis

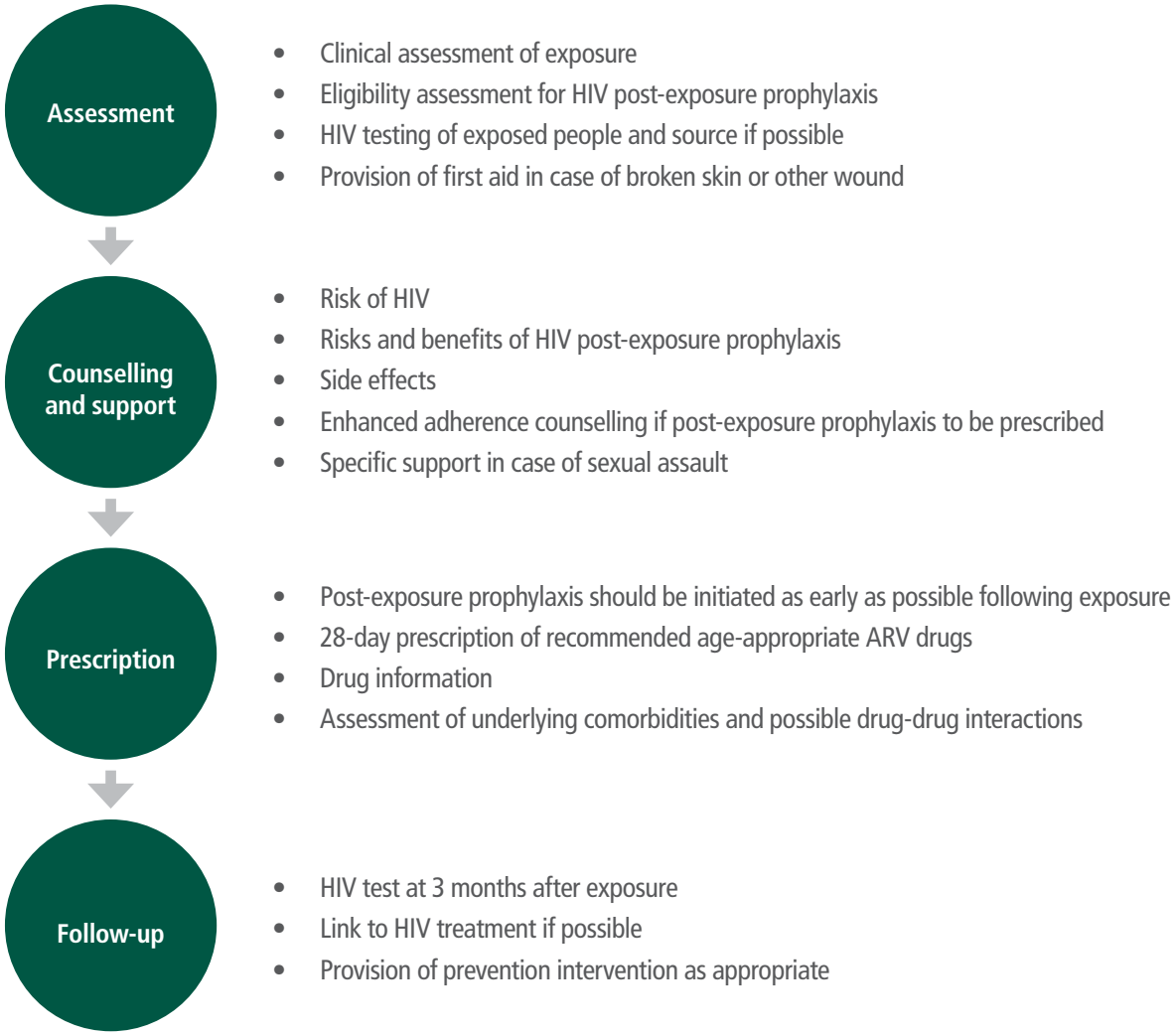
The clinical management guidance outlined in this section is intended for all individuals exposed to a potential HIV source. Subsection 4.11 gives additional guidance for specific populations.

4.1.3.2 Standard of care for individuals exposed to HIV

Everyone possibly exposed to HIV should be assessed by a trained health-care worker. Essential components of the clinical pathway include assessing the mechanism of exposure and assessing eligibility for post-exposure prophylaxis, examination of any wound and initial first-aid treatment (Fig. 4.1). Any prescription of post-exposure prophylaxis should follow consent based on an understanding of the risks and benefits, including discussion of possible side effects and the importance of full adherence to post-exposure prophylaxis.

Baseline testing for HIV and follow-up testing should form part of the clinical pathway but should not delay initiating post-exposure prophylaxis where warranted. Possible exposure to HIV can create significant anxiety for individuals, and counselling support may be required. The importance of primary prevention should also be emphasized as appropriate. In cases that do not require post-exposure prophylaxis, the exposed person should be counselled about limiting future exposure risk, and HIV testing may be provided if desired.

Figure 4.1 Care pathway for people exposed to HIV



4.2 Eligibility for post-exposure prophylaxis

Practical guidance

- Post-exposure prophylaxis should be offered, and initiated as early as possible, to all individuals with exposure that has the potential for HIV transmission, and ideally within 72 hours.[a]
- Assessment for eligibility should be based on the HIV status of the source whenever possible and may include consideration of background prevalence and local epidemiological patterns.[b]
- Exposures that may warrant post-exposure prophylaxis include:
  - parenteral or mucous membrane exposure (sexual exposure and splashes to the eye, nose or oral cavity); and
  - the following bodily fluids may pose a risk of HIV infection: blood, blood-stained saliva, breast-milk, genital secretions and cerebrospinal, amniotic, rectal, peritoneal, synovial, pericardial or pleural fluids.[c]
- Exposures that does not require post-exposure prophylaxis include:
  - when the exposed individual is already HIV positive;
  - when the source is established to be HIV negative; and
  - exposure to bodily fluids that does not pose a significant risk: tears, non-blood-stained saliva, urine and sweat.

[a]Although post-exposure prophylaxis is ideally provided within 72 hours of exposure, people may not be able to access services within this time. Providers should consider the range of other essential interventions and referrals that should be offered to clients presenting after the 72 hours.

[b]In some settings with high background HIV prevalence or where the source is known to be at high risk for HIV infection, all exposure may be considered for post-exposure prophylaxis without risk assessment.

[c]These fluids carry a high risk of HIV infection, but this list is not exhaustive and all cases should be assessed clinically and decisions made by the health-care workers as to whether exposure constitutes significant risk.

4.2.1 Supporting evidence

Data from animal studies suggest that the efficacy of post-exposure prophylaxis in preventing transmission is time dependent *(4,12–15)*, and every effort should be made to provide post-exposure prophylaxis as soon as possible following exposure.

Estimates of the transmission risk per act vary among population groups and are difficult to interpret because of multiple confounding factors *(16)*. The estimated risk of HIV transmission via sexual exposure ranges from 4 per 10 000 exposure incidents for insertive penile-vaginal intercourse to 138 per 10 000 for receptive anal intercourse *(16)*. Percutaneous needle-stick is likely to represent a risk of 23 per 10 000 exposure incidents to an infected source *(16)*. Various factors may influence the risk of transmission including: presence of other sexually transmitted infections in either the source or exposed individual, plasma viral load of the source patient if known to be HIV positive and circumcision status *(17)*.

4.2.2 Assessment of the exposed person's HIV status

Post-exposure prophylaxis is not indicated if the exposed person is already HIV positive. If an individual considered eligible for post-exposure prophylaxis is found to already be HIV positive, they should be referred to appropriate services for assessment for eligibility for ART according to national guidelines.

HIV testing in the context of post-exposure prophylaxis should include initial testing of the exposed individual. HIV testing should be performed using rapid diagnostic tests that can provide definitive results in most cases within 2 hours and often within 20 minutes. HIV testing as in all other situations should be voluntary, and consent for HIV testing should be obtained with standard pre-test and post-test counselling according to national and local protocols. The risks and benefits of testing should be sufficiently explained to the individual so that an informed decision can be made.

Assessment of the HIV status of the exposed individual should not be a barrier to initiating post-exposure prophylaxis. In emergency situations where HIV testing and counselling is not readily available but the potential HIV risk is high or if the exposed person refuses initial testing, post-exposure prophylaxis should be initiated and HIV testing and counselling undertaken as soon as possible.

4.2.3 Assessment of the source person's HIV status

HIV testing of the source person should be conducted to guide appropriate clinical action and inform the exposed individual and, where possible, the source of their HIV status. However, the initiation of post-exposure prophylaxis should not be delayed by the availability of the source HIV test results. In

settings with generalized HIV epidemics, it is reasonable to assume that all sources of unknown HIV status may pose a risk of infection. If the source is determined to be HIV positive, provision should be made to link them to appropriate treatment and care. If the source is established to be HIV negative, post-exposure prophylaxis should be discontinued.

4.2.4 Prescribing and dispensing post-exposure prophylaxis medicine

A 28-day course of ARV drugs should be offered and prescribed following assessment of eligibility for post-exposure prophylaxis. In accordance with ART guidance, trained non-physicians, midwives, nurses and other non-clinical health providers can initiate and dispense ARV drugs for post-exposure prophylaxis *(3)*. Individuals should be aware of the risks and benefits of post-exposure prophylaxis, and verbal consent should be sought. Everyone should be informed of potential drug–drug interactions and possible side effects and toxicity (Annex 1). Promoting adherence is critical to improving completion rates, which are generally low in most populations and settings *(11)*.

4.3 Number of ARV drugs prescribed for post-exposure prophylaxis

Recommendations

A regimen for post-exposure prophylaxis for HIV with two ARV drugs is effective, but three drugs are preferred.

(Conditional recommendation, very-low-quality evidence)

4.3.1 Background

WHO guidelines on post-exposure prophylaxis issued in 2007 *(1)* recommended different post-exposure prophylaxis regimens for different circumstances, with two drugs recommended as standard and the addition of a third drug in situations of known risk of ARV drug resistance in the source person or the community. More recent national guidelines have shifted towards recommending a three-drug regimen for everyone, given the availability of less toxic and better tolerated medications, the difficulty in evaluating the risk of drug resistance and need to simplify prescribing *(18).*

4.3.2 Rationale and supporting evidence

The need to simplify prescribing for post-exposure prophylaxis has been recognized to improve availability by promoting provision by non-specialist health workers and reduce time to initiation. Providing a three-drug ARV regimen to all eligible people is one way to simplify prescribing by removing the requirements to obtain information about drug resistance risk. Providing three drugs for post-exposure prophylaxis is also consistent with recommendations for ART, the standard for which is triple-combination therapy. Although the addition of a third drug increases the potential for drug-related toxicity, reported post-exposure prophylaxis completion rates are similar comparing two- *(19,20)* and three-drug *(21,22)* regimens.

There may be situations where only two-drug regimens are available for post-exposure prophylaxis or where the risk of additional toxicity outweighs the benefit. This is an acceptable option, supported by evidence from animal studies with post-exposure prophylaxis *(23)* as well as other ARV-based prevention interventions, including preventing the mother-to-child transmission of HIV *(8)* and pre-exposure prophylaxis *(9)*.

4.4 Post-exposure prophylaxis ARV regimens – adults and adolescents

Recommendations

TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for adults and adolescents.
(Strong recommendation, low-quality evidence)

LPV/r or ATV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis for adults and adolescents.
(Conditional recommendation, very-low-quality evidence)

Where available RAL, DRV/r or EFV can be considered as alternative options.

4.4.1 Background

Previous WHO guidelines recommended AZT + 3TC as the preferred two-drug regimen *(1)*, in accordance with recommendations for ART at the time *(2)*. Since then, guidelines for ART have evolved towards giving preference to TDF + 3TC (or FTC), since this combination has a better safety profile and price reductions have brought the cost of this regimen in line with the cost of AZT + 3TC. TDF + 3TC (or FTC) is also the preferred regimen for pre-exposure prophylaxis.

4.4.2 Rationale and supporting evidence

The preference for TDF + 3TC (or FTC) for post-exposure prophylaxis is supported by comparative data from randomized trials for ART and pre-exposure prophylaxis and from observational studies with post-exposure prophylaxis. Three randomized trials *(24–26)* comparing TDF + 3TC (or FTC) and AZT + 3TC as part of first-line ART found a significantly lower risk of treatment discontinuation because of adverse events when TDF + 3TC (or FTC) was used (relative risk (RR) = 0.61, 95% confidence interval (CI) 0.51–0.72). For pre-exposure prophylaxis, four randomized controlled trials comparing TDF + FTC and placebo found no statistically significant difference in the risk of severe adverse events (RR = 0.99, 95% CI 0.84–1.16) *(27–30)*.

For post-exposure prophylaxis, data from 15 studies provide information to allow for indirect comparisons between AZT + 3TC (12 studies) *(22,31–41)* and TDF + 3TC (or FTC) (three studies) *(19,42,43)*. Pooled completion rates were 78% (95% CI 66.1–90.7%) for individuals receiving TDF + 3TC (or FTC) and 59% (95% CI 47.2–70.4%) for AZT + 3TC. The rate of post-exposure prophylaxis discontinuation because of an adverse event was lower among individuals taking TDF + 3TC (or FTC) (0.3%, 95% CI 0.0–1.1%) than AZT + 3TC (3.2%, 95% CI 1.5–4.9%).

The recommendation supporting TDF + 3TC (or FTC) is a strong recommendation despite low-quality evidence because of the consistency in the direction of the evidence across different ARV drug interventions and the preference to align the recommendations for post-exposure prophylaxis with the recommendations for ART as far as possible.

The choice of the third drug for post-exposure prophylaxis for adults and adolescents is less clear. Ten studies provide information on lopinavir/ritonavir (LPV/r), atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r) and raltegravir (RAL) as part of three-drug post-exposure prophylaxis *(42–52)*. The small sample size and low quality of these studies do not allow for any clear preference based on tolerability and completion rates, and drug choice is guided by cost, availability and preferences.

Boosted LPV/r or ATV/r are preferred because these drugs are currently recommended for use in ART and relatively widely available in low- and middle-income countries. One small, unpublished study of ATV/r with TDF + FTC for post-exposure prophylaxis was stopped early because participants had a high prevalence of jaundice. Recent published studies have reported good tolerability associated with the use of RAL and DRV/r in post-exposure prophylaxis, but data are limited and, critically, the availability of these drugs remains limited in low- and middle-income countries owing to their higher cost. Several newer drugs, such as dolutegravir, rilpivirine and elvitegravir, have promising features if used as part of a post-exposure prophylaxis regimen (such as high potency and tolerability for dolutegravir, high tolerability of rilpivirine and convenient co-formulation and tolerability for elvitegravir), but given the lack of post-exposure prophylaxis-specific data, no current recommendations for their use can be made.

Efavirenz (EFV) has also been previously recommended for post-exposure prophylaxis and is the preferred third drug for first-line ART. EFV is well tolerated for treatment but has limited acceptability for use for HIV-negative individuals as post-exposure prophylaxis. Although data on the use of EFV for post-exposure prophylaxis are lacking, there are concerns about giving a drug associated with early nervous system and mental events to HIV-negative individuals who may have anxiety related to HIV exposure. For these reasons, EFV is also recommended as an alternative third drug for post-exposure prophylaxis.

Table 4.1 summarizes considerations for choosing a third drug in post-exposure prophylaxis for adults and adolescents.

Table 4.1 Characteristics of third drug options for HIV post-exposure prophylaxis for adults and adolescents

	LPV/r	ATV/r	RAL	DRV/r	EFV
Discontinuation rate in post-exposure prophylaxis *(10)*	7%	21%[a]	2%	6%	No data
Daily dosing	Two tablets twice dailya,[b]	One tablet once daily	One tablet twice daily	One tablet once or twice daily	One tablet once daily
Availability as heat-stable formulation	Yes	Yes	Yes	No	Yes
Accessibility in country (registration status)	High	Low	Low	Low	High
Acceptability by health providers	High	High	High	High	Low
Availability of WHO prequalified generic formulations	Yes	Yes	No	No	Yes

[a]Data only available for ATV/r combined with AZT.

[b]Once-daily dosing can be considered as an alternative for adults but more data are needed for children and adolescents.

4.4.3 Clinical considerations

Despite better tolerability, TDF is associated with a low rate of renal toxicity, especially among people with pre-existing renal disease or risk factors for this. For ART, TDF should be avoided when the estimated glomerular filtration rate is <50 ml/min and among people with long-term diabetes, uncontrolled hypertension or renal failure *(3)*. These considerations may be less important when TDF is used in post-exposure prophylaxis, since the duration of exposure is 28 days.

There is also concern about the potential risk of hepatic flares among people infected with HBV once TDF-, 3TC- or FTC-based post-exposure prophylaxis is stopped, as has been seen for people receiving ART *(53,54)*. Assessment of HBV infection status should not be a precondition for offering TDF-, 3TC- or FTC-based post-exposure prophylaxis, but people with established active HBV infection should be monitored for hepatic flare after discontinuation of TDF-, 3TC- or FTC-based post-exposure prophylaxis if these drugs are not continued for the treatment of HBV. Among people with unknown HBV status and where HBV testing is readily available, people started on TDF-, 3TC-, or FTC-based post-exposure prophylaxis should be tested for HBV to detect active HBV infection and the need for ongoing HBV therapy after discontinuing post-exposure prophylaxis.

Nevirapine should not be used for post-exposure prophylaxis for adults, adolescents and older children because of the risk of life-threatening serious adverse events associated with HIV-negative adults using this drug *(55,56)*.

Table 4.2 summarizes the doses of ARV drugs recommended for use in post-exposure prophylaxis for adults and adolescents. Annex 1 lists the potential adverse drug reactions and drug–drug interactions. For potential adverse reactions, the data are derived primarily from the use of ARV drugs as treatment and reflect both long-term and short-term use.

Table 4.2 Doses of ARV drugs for HIV post-exposure prophylaxis for adults and adolescents

Generic name	Dose
Tenofovir (TDF)	300 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily or 800 mg/200 mg once daily[a]
Atazanavir/ritonavir (ATV/r)	300 mg + 100 mg once daily
Raltegravir (RAL)	400 mg twice daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily or 600 mg + 100 mg twice daily
Efavirenz (EFV)	600 mg once daily

[a]Once-daily dosing can be considered as an alternative for adults, but more data are needed for children and adolescents.

4.5 Post-exposure prophylaxis ARV regimens – children (≤10 years old)

Recommendations

AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for children 10 years and younger.

ABC + 3TC or TDF + 3TC (or FTC) can be considered as alternative regimens.

(Strong recommendation, low-quality evidence)

LPV/r is recommended as the preferred third drug for HIV post-exposure prophylaxis post-exposure prophylaxis for children younger than 10 years.

(Conditional recommendation, very-low-quality evidence)

An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV and NVP.

4.5.1 Background

There is no current WHO guidance for post-exposure prophylaxis ARV drug regimens for children. Paediatric recommendations for treatment of children living with HIV recommend use of ABC + 3TC) as the preferred regimen for children 3–10 years old, and ABC + 3TC and AZT + 3TC are equally recommended for children 3 years and younger *(3)*. TDF + 3TC (or FTC) is included as the alternative option for children 3 years and older, but use is still limited because of concerns about possible bone toxicity. Lack of availability of age-appropriate formulations for children limits regimen choice, and aligning post-exposure prophylaxis recommendations with treatment recommendations and/or with post-exposure prophylaxis regimens for adults could be of value in ensuring availability and reliable procurement for post-exposure prophylaxis.

4.5.2 Rationale and supporting evidence

Evidence from post-exposure prophylaxis observational studies and randomized trials comparing regimens for ART supports the choice of drugs for post-exposure prophylaxis for children.

A systematic review of post-exposure prophylaxis studies identified three prospective cohort studies reporting on AZT + 3TC as part of a two-drug post-exposure prophylaxis regimen for children: 64% (95% CI 41.2–86.8%) of children completed post-exposure prophylaxis and 4% (95% CI 0.4–8.6%) discontinued because of adverse events *(57–59)*. One randomized trial comparing ABC + 3TC and AZT + 3TC as part of first-line ART found no difference in the time to the first serious adverse event between the two arms *(60)*; however, one case of hypersensitivity reaction requiring treatment discontinuation was observed in the ABC + 3TC arm. No randomized evidence was identified to assess direct comparison between TDF + 3TC (or FTC) and ABC- or AZT-containing regimens. Overall, low quality of evidence supports the use of AZT + 3TC as the preferred backbone for post-exposure prophylaxis for children younger than 10 years.

The recommendation favouring AZT + 3TC is strong despite low-quality evidence considering the preference to align drug choices for post-exposure prophylaxis with those for ART, experience in using this regimen for post-exposure prophylaxis for children and cost. AZT and ABC are currently the most commonly used nucleoside reverse-transcriptase inhibitors (NRTIs) as part of triple therapy for children living with HIV, and solid dispersible tablets in combination with 3TC exist for both drugs (formulations of TDF for children are still largely unavailable in most settings).

Comparative evidence on the use of protease inhibitors (PI), non-nucleoside reverse-transcriptase inhibitors (NNRTIs) or integrase strand transfer inhibitors (INSTI) as a third agent for post-exposure prophylaxis or postnatal prophylaxis is lacking. Therefore, the choice of third drug is guided by data from a systematic review of randomized trials for ART comparing LPV/r-based versus NVP-based regimens for treatment-naive children living with HIV *(61)*. This review concluded that the LPV/r-based regimen is superior, with treatment discontinuation 1.8 times less frequent than with an NVP-based regimen (hazard ratio (HR) 1.8, 95% CI 1.3–2.4); however, there was no difference in the frequency of drug-related adverse events *(61)*. For children living with HIV aged 3 years and older, a randomized controlled trial *(62)* did not show any difference in drug-related adverse events requiring treatment discontinuation between the boosted PI versus NNRTI arms. Overall, very low quality of evidence supports the use of LPV/r as the preferred third drug for post-exposure prophylaxis for children younger than 10 years.

LPV/r is the PI most frequently used for children living with HIV because a heat-stable formulation is available for older children. The liquid formulation for use among children will be soon replaced by a heat-stable solid formulation (known as sprinkles). To date, ATV and DRV are not available in generic co-formulation with ritonavir for children. In addition, in contrast to NNRTIs (NVP <3 years and EFV >3 years), LPV/r allows full alignment across age groups and harmonizes third-drug recommendations with the ones in adolescents and adults. Lack of an affordable formulation for RAL for children currently limits the use of this drug for post-exposure prophylaxis despite its favourable efficacy and tolerability profile (Table 4.3).

Table 4.3 Doses of ARV drugs for HIV post-exposure prophylaxis for adults and adolescents

	LPV/r	ATV/r	RAL	DRV/r	EFV	NVP
Discontinuation rate in post-exposure prophylaxis	Low (used for preventing the mother-to-child transmission of HIV)	No data				Low (used for preventing the mother-to-child transmission of HIV)
Daily dosing	Twice daily	Once daily	Twice daily	Once or twice daily	Once daily	Twice daily
Availability as a heat-stable age-appropriate formulation	Yes	No	Yes	No	Yes	Yes
Accessibility in country (registration status)	High	Low	Low	Low	High (>3 years old)	High (all ages)
Acceptability by health providers	High	High	High	High	High	High
Availability of WHO prequalified generic formulations	Yes	Yes	No	No	Yes	Yes
Age indication	>14 days	>3 months	>2 weeks	>3 years	>3 months	<2 years[a]

[a]This age limitation is because of concerns of serious adverse events associated with the use of this drug by HIV-negative adults. NVP has been safely used for HIV-exposed, uninfected infants for preventing the mother-to-child transmission of HIV, but safety data are limited beyond infancy.

4.5.3 Clinical considerations

AZT-associated anaemia has been described both in HIV-exposed infants receiving postnatal prophylaxis and in children living with HIV receiving AZT for treatment, although these changes were mostly mild and transient in nature *(63).* Hypersensitivity reaction to ABC has been described, particularly in Caucasian and Asian children living with HIV. Very low incidence has been reported from a large randomized controlled trial conducted among HIV-positive children in African countries *(64)*.

LPV/r oral liquid should not be used for preterm babies or infants younger than 2 weeks old. In these cases, NVP, which has been widely used for HIV-uninfected infants for preventing the mother-to-child transmission of HIV *(8)*, should be used. However, the NVP toxicity profile beyond infancy remains unclear, and concerns around serious adverse events observed among adults taking NVP as part of post-exposure prophylaxis strongly discourage the use of NVP for post-exposure prophylaxis for children beyond the age of 2 years.

Annex 1 describes toxicity related to ARV drugs and simplified dosing schedules for ARV drugs for post-exposure prophylaxis for children.

4.6 Prescribing frequency

Recommendations

A 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment.

(Strong recommendation, low-quality evidence)

4.6.1 Background

Data from animal studies *(4)* indicate that completing the full course (28 days) of ARV drugs for post-exposure prophylaxis is required to maximize the benefit of the intervention and to prevent seroconversion. Prescribing practices vary in the methods of dispensing ARV drugs following initial risk assessment. Partial prescriptions, often referred to as starter packs and consisting of an initial supply of drugs (3–10 days), have been used as a way to ensure that testing and counselling could be completed before rapid testing techniques became more widely used *(1,65)*. Although non-specialist health-care professionals still dispense a partial prescription in many settings to rapidly initiate post-exposure prophylaxis, the shift towards ART delivery by trained non-physicians, midwives, nurses and other non-clinical health providers has provided sufficient support for all health-care professionals to initiate and dispense the full 28-day course of ARV drugs for post-exposure prophylaxis.

4.6.2 Evidence and rationale for the recommendation

A systematic review was conducted to assess the association between prescribing frequency and post-exposure prophylaxis completion rates *(66)*. Very-low-quality evidence indirectly comparing 54 observational studies found that the proportion of individuals completing a 28-day course of post-exposure

prophylaxis was higher among those receiving the full 28-day prescription of ARV drugs at their initial assessment (70%, 95% CI 56.7–77.3%) than among those receiving partial prescriptions (53%, 95% CI 44.4–82.2%). Refusal rates were also lower in the studies reporting completion rates with a 28-day course: 11% (95% CI 5.3–17.5%) versus 22% (95% CI 16.7–28.1%) for those offered starter packs.

Prescribing the full course at the initial assessment could be considered less resource intensive, since in most cases it may negate the need for a follow-up appointment. Providing a partial prescription with the necessity to return for interim follow-up appointment(s) was considered to be inequitable to populations with limited access to healthcare facilities. In general, starter packs are not recommended as part of routine post-exposure prophylaxis provision and a full course of 28 days of recommended ARV drugs should be provided.

The recommendation to prescribe the full 28-day course of ARV drugs following an initial risk assessment is strong despite very-low-quality evidence considering the need to maximize post-exposure prophylaxis completion rates and simplify prescribing for both the provider and the patient.

4.7 Adherence strategies

Recommendations

Enhanced adherence counselling is suggested for individuals initiating HIV post-exposure prophylaxis.

(Conditional recommendation, moderate-quality evidence)

4.7.1 Background

Adherence to a full 28-day course of ARV drugs for post-exposure prophylaxis is critical to the effectiveness of the intervention. A systematic review of published post-exposure prophylaxis studies demonstrates that completion rates are generally low (56%, 95% CI 50.9–62.2%) for all populations and particularly for adolescents and individuals following sexual assault *(11)*.

Interventions to support adherence and completion of a full post-exposure prophylaxis course are therefore critical. The 2007 WHO HIV post-exposure prophylaxis guidelines suggested counselling as a component of a minimum package of care for post-exposure prophylaxis, and adherence counselling is recommended as a proven way to improve adherence for people living with HIV starting ART *(67)*. Barriers to completing post-exposure prophylaxis are often related to side effects, but other barriers have not been extensively researched.

4.7.2 Evidence and rationale for the recommendation

A systematic review of published post-exposure prophylaxis studies comparing interventions to improve adherence to post-exposure prophylaxis for HIV-negative adults, adolescents and children was conducted. Three randomized controlled trials were identified *(31,36,68)*, all comparing an enhanced form of adherence counselling to standard care. Enhanced adherence interventions studied for post-exposure prophylaxis include baseline individual needs assessment, adherence counselling and education sessions and follow-up telephone calls. The combined estimate of effect on completing a full course of post-exposure prophylaxis showed a tendency towards improved adherence when enhanced counselling was provided (pooled odds ratio (OR) = 1.5, 95% CI 0.9–2.3). Adherence counselling is further supported by studies for ART *(69,70)*. Alternative methods of enhancing adherence were also considered in the WHO ART guidelines *(3)*, and these may be suitable to post-exposure prophylaxis (peer support, alarms, text messages, phone calls and calendars), but the effectiveness of these interventions for HIV-negative individuals in the context of post-exposure prophylaxis has not been evaluated.

4.7.3 Programme considerations

Providing enhanced counselling was considered to be more resource intensive and possibly require increased time, increased resources, including costs to train staff, and monitoring of outcomes. However, current post-exposure prophylaxis completion rates are low in almost all settings, and methods to improve outcomes need to be considered. Similar to routine counselling, the provision of adherence counselling should not delay the initiation of post-exposure prophylaxis. Health workers who are already involved in adherence counselling and patient education could support this task. The timing of initiation of post-exposure prophylaxis is vital, and the time required to deliver any enhanced adherence intervention should not preclude delivery of ARV drugs.

4.8 Management of possible exposure to other conditions

4.8.1 Hepatitis B and C

The risk of transmitting HBV and HCV is higher than the risk of transmitting HIV in most cases of exposure, especially in the health-care setting. Previous HBV vaccination should be assessed and vaccination offered if required according to age-appropriate national immunization schedules *(71)*. Hepatitis B immunoglobulin protects by passive immunization if given shortly after exposure and should be considered if available for unvaccinated or partly vaccinated individuals in addition to vaccination.

Screening for HCV should be offered in accordance with WHO guidelines *(72)*. Individuals should be counselled on the risk of acquiring HCV and be referred to specialist care if seroconversion occurs.

4.8.2 Sexually transmitted infections

Exposure to sexually transmitted infections will often co-exist with HIV exposure through sexual routes. Screening, diagnosis and presumptive treatment of sexually transmitted infections should follow established guidelines *(73–75)*.

4.8.3 Pregnancy

All women should be offered pregnancy testing at baseline and follow-up. Emergency contraception should be offered to girls and women as soon as possible and within 5 days following sexual exposure *(74,75)*.

4.8.4 Tetanus

Individuals who sustain wounds (bites, abrasions or cuts) should have their tetanus status assessed and be offered immunization if indicated according to WHO guidelines *(76)*.

4.9 Follow-up

4.8.1 Hepatitis B and C

A follow-up appointment for people prescribed post-exposure prophylaxis should be scheduled for a repeat HIV test 3 months following HIV exposure. Review of an individual during the 28-day period is not essential, but individuals should be encouraged to seek assistance if they experience side effects that interfere with taking ARV drugs or adherence problems. Any further contact with a person prescribed post-exposure prophylaxis should emphasize the importance of completing the full 28-day course, and reducing future risk of HIV infection. If the source is established to be HIV negative during the course of post-exposure prophylaxis, ARV drugs can be discontinued.

4.9.1 HIV testing

All individuals potentially exposed to HIV should be encouraged to undergo HIV testing 3 months following exposure.

Further testing after this time should be in accordance with WHO retesting and counselling guidelines *(77)* and may be warranted for people with an HIV-negative test result who:

- have ongoing high-risk HIV behaviour;
- can identify a specific incident of HIV exposure in the past 3 months;
- are pregnant and residing in a generalized HIV epidemic setting; or
- have an indeterminate HIV status.

4.9.2 Linkage to HIV care and treatment

Individuals diagnosed with HIV following post-exposure prophylaxis should be linked to treatment and care services as soon as possible following a positive HIV test result, according to WHO *(3)* and national guidelines. Any source person confirmed to be HIV positive should be linked to HIV treatment programmes.

4.10 Prevention

Chronic exposure to HIV can occur in many settings. In all scenarios, an individual's exposure pattern should be assessed and primary prevention emphasized.

In certain situations of chronic exposure, consideration should be given to offering pre-exposure prophylaxis. WHO guidelines *(78)* recommend providing pre-exposure prophylaxis to men who have sex with men as part of the package of combination prevention interventions. Discussing pre-exposure prophylaxis as a prevention option may also be suitable for other population groups following individual assessment. In all cases, the full range of prevention strategies should also be considered and discussed.

4.10.1 Secondary prevention while taking post-exposure prophylaxis

Counselling to reduce the risk of further HIV transmission is necessary to prevent transmission to sexual partners and the children of breastfeeding mothers (see section 4.11.1.3). Risk reduction counselling should form part of each consultation with the individual. The use of condoms and safe injecting practices to prevent secondary transmission should be discussed. Blood donation should be avoided while individuals are taking post-exposure prophylaxis following a possible HIV exposure and while still in the window period for HIV acquisition and testing.

4.11 Considerations for specific populations

4.11.1 Health care workers

Health-care workers are at significant risk of HIV, HBV and HCV infections through exposure in occupational settings. The frequency of exposure may be underreported, and all efforts should be made to encourage health-care workers to report exposure to their supervisors. Primary prevention advice should include universal precautions and safe injection practices to prevent injuries and secondary transmission in accordance with workplace policies on HIV *(79)*. The risk of transmitting HBV and HCV is much higher than the risk of transmitting HIV in health-care settings, and other measures should be considered, including routine vaccination against HBV and HBV immunoglobulin where appropriate following exposure. Follow up for health-care workers should respect confidentiality, and reporting and recordkeeping should be in accordance with national occupational health policies *(80)*.

4.11.2 Survivors of sexual assault

Women subjected to intimate partner violence should receive post-exposure prophylaxis as part of a broader care package of care, including first-line support, emergency contraception and prophylaxis for sexually transmitted infections in combination with psychological interventions according to recently updated WHO guidelines *(81)*. Other people who have been sexually assaulted, including men, children and adolescents, need to have psychosocial issues considered in combination with post-exposure prophylaxis, as part of the standard package of care. Care should be taken to ensure referral to appropriate services and multidisciplinary team involvement in combination with adherence support.

4.11.3 Other considerations

4.11.3.1 Pregnant and lactating women

None of the current ARV drug regimens recommended for post-exposure prophylaxis are contraindicated for pregnant women. Breastfeeding should not contraindicate post-exposure prophylaxis, but the risks and benefits of continuing breastfeeding while HIV transmission risk is unknown should be discussed with the mother.

4.11.3.2 Children

HIV testing approaches for infants and children should be performed in accordance with WHO HIV testing guidelines *(3,82)*, with serological testing followed by confirmatory virological testing for infants <18 months of age. If an infant is HIV negative but with possible exposure from a maternal source, repeat testing should be completed 6 weeks or more after breastfeeding ends.

Informed consent by a parent or guardian is required for all testing and offering post-exposure prophylaxis for infants and children. Weight-based dosing for ARV drug formulations should be guided by the WHO ART guidelines (Annex 1) *(3)*.

Children who are exposed to sexual assault should also receive prophylaxis for sexually transmitted infections and emergency contraception.

4.11.3.3 Adolescent

Requiring parental consent for adolescents is recognized as a barrier to HIV testing, particularly in cases of sexual assault. HIV testing should be performed in accordance with national consent policies and follow the principles of care local to the country context *(83)*. Adherence support is a priority, considering the currently reported low completion rates.

4.12 Research gaps

Table 4.4 summarizes the key research priorities identified in developing these guidelines.

Table 4.4 Research priorities for the use of ARV drugs as HIV post-exposure prophylaxis

	LPV/r
Access	• Understanding barriers to accessing post-exposure prophylaxis for all population groups • Feasibility and outcomes of delivering post-exposure prophylaxis in various health care settings, including by non-physician providers
Drug choice	• Research to inform future ARV drug choices for adults, adolescents and children • Efficacy in preventing infection, including considering ARV drug penetration levels in cervicovaginal and anal tissues • Toxicity monitoring • Drug–drug comparisons • Resistance profiling and regimen selection • Drug–drug interactions specific to post-exposure prophylaxis • The potential use of newer ARV drugs (dolutegravir, rilpivirine, low-dose EFV, elvitegravir, maraviroc and vicraviroc) for post-exposure prophylaxis • HBV flare risk with the short-course use of TDF, 3TC and FTC
Adherence	• Optimal adherence interventions, including specific interventions for populations at high risk of poor adherence • Impact of the pill burden on adherence to post-exposure prophylaxis
Follow-up	• Optimal testing strategies at follow-up for HIV and other types of exposure • Strategies and impact of transitioning from post-exposure prophylaxis to pre-exposure prophylaxis • Managing interruptions of post-exposure prophylaxis

4.13 Guidance for programme managers: implementing the key recommendations

Decisions regarding the implementation of these recommendations should be made through a transparent, open and informed process. National programmes should consider linking to existing HIV technical working groups to support the updating, consolidation and dissemination of new guidance on post-exposure prophylaxis. The role of the guideline group may include reviewing current practice and outcomes related to post-exposure prophylaxis; interpreting global and local evidence related to the new recommendations within the local context; and identifying implementation issues such as costs, human resource and infrastructure requirements and how these should be addressed.

Global and national commitments require providing HIV treatment and prevention to everyone in need, following the human rights principles of non-discrimination, accountability and participation. Key ethical principles of fairness, equity and urgency should also be observed in the process of reviewing and adapting guidelines. The design of effective and equitable policies implies that strategies should focus comprehensively on addressing barriers to access testing, prevention and treatment services, particularly those faced by key populations.

The budgetary, human resource requirements and other health system implications of implementing these updated recommendations should be determined to identify which inputs and systems are currently available and which areas require additional investment.

Cost and cost–effectiveness analysis may help inform decisions around drug choice. WHO has issued technical guidance to support planned transition to new regimens for ART, and many of the recommendations apply equally to changes in drug use for post-exposure prophylaxis *(82)*.

An implementation plan should clearly define the set of activities required in a specified period of time to achieve targeted outcomes, with a clear division of labour among all stakeholders involved in implementing programmes, including non-HIV services involved in post-exposure prophylaxis provision (especially emergency services).

4.14 Monitoring and evaluation

Monitoring and evaluation will help programme managers to assess the effectiveness of post-exposure prophylaxis delivery, identify where problems are occurring from eligibility assessment to follow–up after post-exposure prophylaxis and develop effective mechanisms to improve programming. Monitoring individual and population-level outcomes, including adverse drug reactions and seroconversions as a result of the failure of post-exposure prophylaxis, is also essential to assess the impact of post-exposure prophylaxis. Data can be collected in various ways, including routinely reported data from all facilities or sentinel sites; population-based surveys; surveillance data; observations on cohorts of people eligible for post-exposure prophylaxis; and periodic evaluation. Qualitative surveys can provide a valuable complement to routine data collection to inform barriers to accessing and completing post-exposure prophylaxis from a beneficiary perspective.

Data collection should form part of other existing data collection systems and be linked to national registries. A national registry of exposure, post-exposure prophylaxis prescription and outcome will enable the evaluation of new recommendations and revised policies. Guidance is available from WHO on the monitoring and evaluation of ARV drug use, including surveillance of ARV drug toxicity monitoring and surveillance of drug resistance *(82)*.

Information held in data management systems should be kept confidential. Annex 1 outlines the suggested key indicators for evaluating integration of post-exposure prophylaxis in HIV programmes.

5. THE USE OF CO-TRIMOXAZOLE PROPHYLAXIS FOR HIV-RELATED INFECTIONS AMONG ADULTS, ADOLESCENTS AND CHILDREN

Supplementary section to the 2013 WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, Chapter 8 – Prevention, screening and management of common coinfections

5.1 Background

Co-trimoxazole is a fixed-dose combination of two antimicrobial drugs (sulfamethoxazole and trimethoprim) that covers a variety of bacterial, fungal and protozoan infections. Co-trimoxazole preventive therapy is a feasible, well tolerated and inexpensive intervention for people living with HIV to reduce HIV-related morbidity and mortality *(1).* Further, co-trimoxazole is an off-patent drug and widely available in resource-limited settings. In 2006, WHO guidelines on co-trimoxazole prophylaxis in resource-limited settings *(2)* were issued. The guidelines recommend co-trimoxazole prophylaxis to be implemented as an integral component of the HIV care package. Importantly, these guidelines noted the effectiveness of co-trimoxazole prophylaxis in reducing mortality and morbidity across varying levels of background resistance to co-trimoxazole and the prevalence of malaria. The expanded access and progressive movement towards earlier initiation of ART warranted an update to existing WHO guidelines on co-trimoxazole prophylaxis.

5.2 Co-trimoxazole prophylaxis for adults

- Co-trimoxazole prophylaxis is recommended for adults (including pregnant women) with severe or advanced HIV clinical disease (WHO stage 3 or 4) and/or with a CD4 count of ≤350 cells/mm^3.

(Strong recommendation, moderate-quality evidence)

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be initiated regardless of CD4 cell count or WHO stage.

(Conditional recommendation, moderate-quality evidence)

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

(Conditional recommendation, low-quality evidence)

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued regardless of CD4 cell count or WHO clinical stage.

(Conditional recommendation, moderate-quality evidence)

- Routine co-trimoxazole prophylaxis should be administered to all HIV-infected people with active TB disease regardless of CD4 cell counts.

(Strong recommendation, high-quality evidence)[a]

[a]Recommendation maintained from *WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders (49).*

5.2.1 Rationale and supporting evidence for the use of co-trimoxazole prophylaxis for adults

5.2.1.1 When to start co-trimoxazole prophylaxis

Moderate-quality evidence from nine observational studies *(3–11)* supports the effectiveness of co-trimoxazole prophylaxis in reducing mortality risk among people starting ART with a CD4 cell count ≤350 cells/mm3. Overall, the GRADE assessment suggested limited risk of bias, imprecision and indirectness in this body of observational literature. One study *(11)* also reviewed other outcomes and found a reduction in WHO stage 3 or 4 events (low-quality evidence) and malaria (low-quality evidence) and a low rate of treatment-limiting adverse events (low-quality evidence). Another study *(7)* found comparable rates of *Pneumocystis jirovecii* pneumonia (very-low-quality evidence).

A second GRADE assessment examined four studies of adults not on ART and with CD4 cell counts >350 cells/mm^3

(12–15). In one randomized controlled trial *(12)*, co-trimoxazole prophylaxis was shown to reduce the rates of new WHO stage 3 or 4 clinical events (high-quality evidence), severe bacterial infections (high-quality evidence), malaria (high-quality evidence) and hospitalization (high-quality evidence). Rates of TB, death and bacterial pneumonia were also reduced, but these effect estimates did not reach statistical significance (moderate-quality evidence). Finally, the rate of treatment-limiting adverse events was also low in this trial (high-quality evidence). Three observational studies reported a reduction in malaria (moderate-quality evidence).

The Guideline Development Group reasoned that the clinical benefits outweighed the additional pill burden and possible cost associated with co-trimoxazole prophylaxis. The Guideline Development Group also judged that co-trimoxazole prophylaxis was acceptable to health-care workers and the community living with HIV. The Guideline Development Group acknowledged operational feasibility and determined that there were no major barriers to uptake of this new WHO recommendation on initiating co-trimoxazole prophylaxis. Considering all these domains, the Guideline Development Group agreed on the initiation recommendations in adults.

5.2.1.2 When to stop co-trimoxazole prophylaxis

The risks and benefits of continuing versus stopping co-trimoxazole prophylaxis after immune recovery above 350 CD4 cells/mm^3 were assessed. Two randomized trials *(16,17)* found that continuing co-trimoxazole reduced hospitalization, malaria, pneumonia and diarrhoea in settings where malaria and/or serious bacterial infections were highly prevalent (high-quality evidence). The rates of mortality and new stage 3 or 4 events were comparable in the study arms (moderate and low-quality evidence, respectively).

The risks and benefits of continuing versus stopping co-trimoxazole prophylaxis after viral suppression induced by ART were also evaluated in settings with a low burden of malaria and serious bacterial infections. Two studies *(18,19)* found that the rates of *Pneumocystis jirovecii* pneumonia and death were similar among people receiving ART who achieved viral suppression and had CD4 cell counts above 100 cells/mm^3 in study arms. Guidelines are available from high-income countries to inform practice in these settings *(20,21)*.

The Guideline Development Group determined that maintaining co-trimoxazole prophylaxis confers clinical benefits that outweigh the potential risks. The recommendation for settings with a high prevalence of malaria and/or severe bacterial infections may simplify HIV management, forecasting and supply management issues and improve co-trimoxazole prophylaxis access to people living with HIV. The Guideline Development Group also recognized that HIV-uninfected people may have a potential disadvantage in terms of diarrhoea, pneumonia and malaria prevention over people who are infected with HIV and receiving co-trimoxazole. Given all these factors, the Guideline Development Group agreed on the discontinuation recommendations for adults using some clinical, immunological and virological parameters indicating immune recovery resulting from ART. However, in settings with a low prevalence of malaria and/or severe bacterial infections and limited or no access to CD4 testing, co-trimoxazole prophylaxis should not be discontinued.

5.2.2 Co-trimoxazole prophylaxis in pregnancy

In the 2006 guidelines, WHO *(2)* recommended that co-trimoxazole prophylaxis be initiated and maintained regardless of the stage of pregnancy in eligible women living with HIV. There have been concerns that folate depletion resulting from the use of co-trimoxazole (as well as sulfadoxine and pyrimethamine, which are commonly used for malaria prophylaxis) during pregnancy may result in an increased risk of teratogenicity *(22,23)*. A systematic review identified 24 studies that evaluate co-trimoxazole use among women irrespective of HIV status, trimester of pregnancy, or purpose of use. The findings of this review support continued recommendations for co-trimoxazole as a priority intervention for HIV-infected pregnant women *(24)*. Given the low quality of this evidence, the heterogeneity of results in studies and possible confounding (the reporting of folate supplementation is inconsistent), the Guideline Development Group could not conclude that co-trimoxazole exposure increases the risk of teratogenicity and that the benefits outweighed any potential risk. The Guideline Development Group endorsed the need to promote pregnancy registries and toxicity monitoring.

WHO recommends the intermittent preventive treatment of malaria in pregnancy[1] in settings with moderate-to-high malaria transmission (where malaria prevalence exceeds 10% among children 2–9 years old) *(25)*. A systematic review identified two randomized trials *(26,27)*, which found co-trimoxazole prophylaxis to be non-inferior to intermittent preventive treatment of malaria in pregnancy with respect to infant mortality, low birth weight (<2.5 kg), placental malaria, maternal death and treatment-limiting adverse events (high-quality evidence). Non-inferiority for clinical malaria could not be concluded (low-quality evidence). Based on these data, the Guideline Development Group determined that co-trimoxazole prophylaxis for pregnant women with HIV can be used to prevent malaria among infants and that pregnant women with HIV should follow the same principles as adults with HIV. Intermittent preventive treatment of malaria in pregnancy should not be provided in addition to co-trimoxazole prophylaxis.[2]

5.2.3 Dosing adults

The recommended dose of co-trimoxazole for adults living with HIV is 960 mg daily (800 mg sulfamethoxazole + 160

1. Intermittent preventive treatment of malaria in pregnancy provides antimalarial drugs to pregnant women at each scheduled antenatal care visit to reduce the complications of malaria in the infant and the mother.

2. Co-trimoxazole prophylaxis is dosed daily not intermittently.

mg trimethoprim, either as a 960-mg double-strength tablet or two 480-mg single-strength tablets). A systematic review examined whether a lower dose of co-trimoxazole (480 mg daily) could provide the same efficacy as 960 mg in preventing a broad spectrum of HIV-related infections. Two trials *(28,29)* found 480 mg to be non-inferior to 960 mg with respect to death, *Pneumocystis jirovecii* pneumonia, toxoplasmosis, malaria, pneumonia and diarrhoea. However, there was no consistent reduction in treatment-limiting adverse events. The Guideline Development Group recommended maintaining 960 mg daily and recognized that further clinical and toxicity data are needed to propose a reduction in co-trimoxazole dose.

5.3 Co-trimoxazole prophylaxis for HIV-infected infants, children and adolescents3

- Co-trimoxazole prophylaxis is recommended for infants, children and adolescents with HIV, irrespective of clinical and immune conditions. Priority should be given to all children younger than 5 years old regardless of CD4 cell count or clinical stage and children with severe or advanced HIV clinical disease (WHO clinical stage 3 or 4) and/or those with a CD4 count of ≤350 cells/mm^3.

(Strong recommendation, high-quality evidence)

- In settings where malaria and/or severe bacterial infections are highly prevalent, co-trimoxazole prophylaxis should be continued until adulthood irrespective of whether ART is provided.

(Conditional recommendation, moderate - quality evidence)

- In settings with low prevalence for both malaria and bacterial infections, co-trimoxazole prophylaxis may be discontinued for children 5 years of age and older who are clinically stable and/or virally suppressed on ART for at least 6 months and with a CD4 count >350 cells/mm^3.

(Strong recommendation, very-low-quality evidence)

5.3.1 When to start co-trimoxazole prophylaxis

The existing evidence analysed though GRADE assessment supports the expansion of the initiation of co-trimoxazole prophylaxis to children with CD4 cell counts above the current threshold. These new recommendations were informed by the CHAP trial in Zambia, a double-blind, placebo-controlled randomized trial *(30–33)*, which was interrupted because of sustained benefit in the co-trimoxazole prophylaxis group. This study found a 43% reduction in mortality irrespective of age and CD4 cell count at randomization (follow-up of median 1.9 years) ($P = 0.0002$) and co-trimoxazole prophylaxis was also associated with reduced rates of hospitalization *(34)*. Of note, hospitalization associated with severe bacterial infections was the most common, even though there were overall few events for malaria and severe bacterial infections *(35)*. Grade 3 or 4 adverse events were limited, with no significant difference across arms *(30)*.

The CHAP trial has demonstrated overall that providing co-trimoxazole prophylaxis to children has survival benefit irrespective of age and CD4 cell count in settings where severe bacterial infections and/or malaria are highly prevalent. However, the Guideline Development Group acknowledged that most children in the CHAP trial, being immunocompromised, already met the criteria for initiating co-trimoxazole prophylaxis and recognized the uncertainty around the generalizability of these findings to children whose CD4 cell counts are higher by downgrading the quality of the evidence for indirectness and imprecision.

The Guideline Development Group considered the value of giving priority to children with advanced disease and immunosuppression to better reflect the quality of the evidence and to harmonize with adult recommendations, which was also considered important. Although there may be potential issues with the acceptability of the intervention, the individual and programmatic benefits of these revised recommendations appeared to outweigh the risks. In addition, providing co-trimoxazole prophylaxis to all children and adolescents was considered to be feasible given the low price of co-trimoxazole prophylaxis and the limited additional infrastructure needed to deliver co-trimoxazole prophylaxis *(32)*. Overall, the strength of the recommendation was ranked as strong.

5.3.2 When to stop co-trimoxazole prophylaxis

The ARROW trial, a randomized, open-label non-inferiority trial undertaken in Uganda and Zimbabwe in 758 children 3 years and older who were receiving ART for at least 96 weeks *(36)*, informed the recommendation on discontinuation made by the Guideline Development Group. Over a median of 2.1 years of follow-up of children and adolescents receiving ART, with median a CD4 cell count of 720 cells/mm^3 (among those older than 5 years) and CD4 percentage of 33%, continuing co-trimoxazole prophylaxis was associated with fewer "deaths or hospitalization", and this effect was sustained over time and was observed in settings with and without malaria. Continuing co-trimoxazole prophylaxis was safe over the same follow-

3.WHO 2006 guidelines *(2)* recommended daily co-trimoxazole prophylaxis for HIV-infected children <2 years old and for those >2 years old with symptomatic disease or CD4 cell counts below age-related thresholds, but state that children >5 years old with good adherence after >6 months on ART, full clinical recovery and CD4 >350 cells/mm^3 may discontinue.

up period, and no severe drug-related adverse events were observed *(36)*.

The systematic review supports continuing co-trimoxazole prophylaxis throughout childhood, based on randomized trial data, which were considered to provide moderate-quality evidence. However, because long-term data on the benefits and potential toxicity are lacking, some uncertainty was observed around acceptability and the balance between risks and benefits. The feasibility and the cost implications of extending co-trimoxazole prophylaxis throughout childhood was not of concern, since the ARROW trial showed that continuing co-trimoxazole prophylaxis improved health outcomes at reduced costs (by reducing hospitalization). Overall, the strength of the recommendation was ranked as conditional.

In settings with a low prevalence of both malaria and severe bacterial infections and where the use of co-trimoxazole prophylaxis has the main goal of preventing *Pneumocystis jirovecii* pneumonia, the Guideline Development Group agreed that discontinuation could be considered. It was supported by the evidence from two observational studies *(37,38)*[4] conducted in Europe and the United States of America suggesting that co-trimoxazole prophylaxis could be safely discontinued in children and adolescents living with HIV with a CD4 count above 200 cells/mm^3. These studies, combined with the opportunistic nature of *Pneumocystis jirovecii* pneumonia. which very rarely affects individuals without severe immune suppression, set the foundation for the existing clinical recommendations for the use of co-trimoxazole for children living with HIV in high-income countries *(39,40)*, where interrupting co-trimoxazole with a CD4 count above 200 cells/mm^3 has become clinical practice for almost a decade.

5.3.3 Dosing for children

The dosing of co-trimoxazole prophylaxis for children is optimized based on body weight bands (Annex 2). No robust evidence was identified that would warrant a change to the current dosing recommendations for children *(30,31,41)*.

5.4 Co-trimoxazole prophylaxis for HIV-exposed infants

- Co-trimoxazole prophylaxis is recommended for HIV-exposed infants 4–6 weeks of age and should be continued until HIV infection has been excluded by an age-appropriate HIV test to establish final diagnosis after complete cessation of breastfeeding.

(Strong recommendation, very-low-quality evidence)

Several factors since 2006 have warranted new recommendations on the use of co-trimoxazole prophylaxis in HIV-exposed infants, particularly with increasing effectiveness of preventing the mother-to-child transmission of HIV interventions. In settings where the coverage of services for preventing the mother-to-child transmission of HIV and early infant diagnosis are both high, there are questions as to whether co-trimoxazole prophylaxis provides any added benefit for HIV-exposed uninfected infants who are breastfed *(42)*. Nevertheless, higher morbidity and mortality reported for HIV-exposed uninfected infants compared to unexposed infants, including increased susceptibility to Pneumocystis jirovecii pneumonia, has been reported *(43)*.

The group considered that the evidence of clinical benefit for HIV-exposed uninfected infants who are not at risk of acquiring HIV infection is insufficient to recommend the use of co-trimoxazole prophylaxis in this population. Although the benefit demonstrated by randomized evidence *(44)* in reducing malaria incidence was recognized, the Guideline Development Group decided to maintain the existing recommendation in face of alternative interventions (malaria intermittent preventive treatment for infants, bed-nets and pneumococcal and rotavirus vaccine) that are currently being implemented to prevent malaria, pneumonia and diarrhoea among children without HIV. The existing recommendation was simplified in language, and both the strength of the recommendation and the quality of evidence have now been defined.

Given the rationale for providing co-trimoxazole prophylaxis in breastfed infants who could potentially become infected, the evidence to support this recommendation is derived from the CHAP trial, which demonstrated a benefit in survival for children initiating co-trimoxazole prophylaxis. This evidence was downgraded for indirectness and was considered of very low quality for the use of co-trimoxazole among HIV-exposed infants. However, this intervention is considered safe and extremely valuable during the period with the highest HIV-related mortality in the first 2 years of life. Given the very low coverage of infant testing and the existing challenges in ensuring the timely identification and linkage of infants living with HIV, particularly those acquiring HIV infection during breastfeeding, no major uncertainty in terms of risks, acceptability and feasibility was detected, and the strength of recommendation was thus ranked as strong. In summary, co-trimoxazole prophylaxis should be started for all HIV-exposed infants but not be continued after the period during which HIV-exposed uninfected infants have a risk of acquiring HIV infection.

5.5 Implementation considerations

Some of the major barriers to implementing co-trimoxazole prophylaxis include (a) supply chain and management issues leading to stock-outs; (b) imposing user charges for medication and/or monitoring; (c) inadequate training, supervision and/or mentoring of health-care workers; (d) low coverage levels of HIV testing and counselling; and (e) lack of coordination across programmes. National programmes could implement co-trimoxazole prophylaxis policy and guidelines more effectively through various mechanisms (Box 5.1).

Box 5.1 How to improve the implementation of policy and guidelines on co-trimoxazole prophylaxis at the national level

- Adapt WHO guidelines to the national context
- Strengthen national and local drug supply management systems to ensure the sustained availability of co-trimoxazole at health care facilities
- Secure funding for providing co-trimoxazole prophylaxis to ensure that no user charges for co-trimoxazole are imposed
- Coordinate with malaria programmes at the country level regarding recommendations related to the intermittent preventive treatment of malaria in pregnancy and seasonal malaria chemoprophylaxis for children younger than 5 years
- Provide co-trimoxazole prophylaxis to eligible people at TB, maternal, newborn and child health and opioid substitution therapy services
- Scale up the training and sensitization of health care workers
- Increase co-trimoxazole prophylaxis knowledge at the community level
- Ensure that a human rights framework is used: for example, people with HIV should always consent to using co-trimoxazole prophylaxis
- Ensure that high-quality co-trimoxazole formulations are provided
- Monitor the toxicity of adverse reactions, particularly in chronic use of co-trimoxazole prophylaxis
- Assess adherence to policies and the impact on population health

5.6 Research gaps

Future research is essential to better understand the long-term safety of and adherence to co-trimoxazole prophylaxis in all populations. Examining barriers to co-trimoxazole prophylaxis adherence into adolescence, and eventually into adulthood, will help optimize the management of HIV infection. Further research is also needed on the benefits and risks among people with high CD4 cell counts receiving ART. For example, the effect of co-trimoxazole prophylaxis for both adults and children receiving ART who then develop TB needs to be examined.

Since introducing co-trimoxazole prophylaxis early to HIV-exposed uninfected infants might cause gut perturbations and affect the gut microbiome, the Guideline Development Group recognized that research could inform how infant immunity is affected. Further, the Guideline Development Group recommended future studies using animal models and clinical studies in humans to address co-trimoxazole toxicity. Future studies are also needed to assess the safety and appropriate dosing of co-trimoxazole prophylaxis in neonates (<4 weeks of age), for whom co-trimoxazole prophylaxis is not currently recommended because of potential kernicterus. A review of the evidence *(45)* has shown that co-trimoxazole prophylaxis among neonates is unlikely to cause kernicterus. Animal models and clinical studies could better inform the safety of initiating co-trimoxazole prophylaxis when infants are diagnosed with HIV soon after birth.

More surveillance of co-trimoxazole prophylaxis use during pregnancy and breastfeeding is also required. The Guideline Development Group emphasized the need to measure birth outcomes, birth defects and toxicity in infants. Although the systematic review of dosing studies in adults demonstrated the non-inferiority of lower dose, adequately powered studies are needed to improve confidence in the size of the effect for death and treatment-limiting adverse events. Although co-trimoxazole is well tolerated with low rates of toxicity, skin rash (including Stevens-Johnson syndrome), reactions of the blood and blood-forming organs and liver toxicity have been reported. Future studies could help identify the people at

highest risk of developing hypersensitivity and severe toxicity.

The Guideline Development Group also suggested that future co-trimoxazole research should explore the cost–effectiveness and acceptability among people with HIV (Table 5.1). Although co-trimoxazole has been shown to be effective in settings with high levels of co-trimoxazole resistance, understanding whether people living with HIV using co-trimoxazole affects community co-trimoxazole resistance and whether community co-trimoxazole resistance affects treatment failure for other infectious diseases is important for national efforts to combat antimicrobial resistance. The use of a fixed-dose combination of co-trimoxazole + isoniazid + pyridoxine should also be explored where large proportions of people living with HIV are eligible for these medications (Table 5.2). Lastly, co-trimoxazole's potential anti-inflammatory properties may have a role in HIV therapy, and this warrants more research *(46)*.

Table 5.1 Criteria for initiating and discontinuing co-trimoxazole prophylaxis

Population	Recommendations	
	Criteria for initiating co-trimoxazole prophylaxis	Criteria for discontinuing co-trimoxazole prophylaxis
Adults (including pregnant women) with HIV	Initiate in everyone with severe or advanced HIV disease (WHO clinical stage 3 or 4) or CD4 ≤350 cells/mm^3[a] In settings with high prevalence of malaria and/or severe bacterial infections[b]: initiate for everyone regardless of WHO clinical stage or CD4 cell count	May be discontinued for those who are clinically stable[c], with evidence of immune recovery and/or viral suppression on ART[d,e] In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued
Children and adolescents with HIV	Initiate for everyone regardless of WHO clinical stage or CD4 cell count As a priority: (1) initiate for everyone younger than 5 years regardless of WHO clinical stage or CD4 cell count; (2) initiate for everyone older than 5 years with severe or advanced HIV disease (WHO clinical stage 3 or 4) or a CD4 count ≤350 cells/mm^3	In settings with a high prevalence of malaria and/or severe bacterial infections: should be continued until adulthood In settings with a low prevalence of both malaria and severe bacterial infections: may be discontinued for those older than 5 years who are clinically stable, with evidence of immune recovery[f] and/or viral suppression on ART
HIV-exposed but uninfected infants	Initiate for everyone starting at 4–6 weeks after birth	Until the risk of HIV transmission ends or HIV infection is excluded[g]
People living with HIV and TB[h]	Initiate for everyone with active TB regardless of CD4 cell count	Until adult or children criteria for discontinuation are met

[a] This group is also given priority for ART initiation (as recommended for ART in the 2013 WHO consolidated guidelines *(47)*.

[b] Settings in which malaria and/or severe bacterial infections are highly prevalent include low- and middle-income countries with high rates of mortality for children younger than 5 years old [(48)].

[c] Clinically stable adults are defined as individuals receiving ART for at least 1 year without any new WHO clinical stage 2, 3 or 4 events.

[d] CD4 count >350 cells/mm^3, with viral load suppression, is considered immune recovery (some countries may adopt a threshold of CD4 count >500 cells/mm^3).

[e] WHO recognizes that, in settings with a low prevalence of malaria and severe bacterial infection settings where co-trimoxazole is used primarily as prophylaxis for some HIV-associated opportunistic infections (*Pneumocystis jirovecii* pneumonia and toxoplasmosis), guidelines exist for discontinuing co-trimoxazole in adults with HIV infection when there is evidence of viral suppression and immune recovery at a CD4 count >200 cells/mm^3 and they have been receiving ART for at least 1 year.

[f] Parameter for immune recovery among children >5 years old: CD4 count >350 cells/mm^3, with viral load suppression.

[g] In settings with high malaria transmission, consideration may be given to extending co-trimoxazole prophylaxis among HIV-exposed uninfected infants up to 2 years of age.

[h] Recommendation maintained from *WHO policy on collaborative TB/HIV policy activities: guidelines for national programmes and other stakeholders (49)*.

Table 5.2 Simplified dosing of co-trimoxazole prophylaxis for children

Drug	Strength of tablet or oral liquid (mg or mg/5 ml)	Number of tablets or ml by weight band once daily					
		3.0–5.9 kg	6.0–9.9 kg	10.0–13.9 kg	14.0–19.9 kg	20.0–24.9 kg	25.0–34.9 kg
Co-trimoxazole	Suspension 200/40 mg per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	1

6. DISSEMINATION OF THE SUPPLEMENT

The guidelines will be disseminated as a printed publication and electronically on the WHO website in the official United Nations languages. The web version will include all annexes. A short version will summarize key new and existing recommendations for easy reference. A library of all supporting documentation and evidence will also be made available on the website in the form of annexes. WHO headquarters will work closely with regional and country offices and implementing partners to ensure their wide dissemination through regional and subregional meetings. Assistance will be provided to Member States to adapt the guidelines to their national contexts.

An evaluation of how users have implemented the guidelines has been developed to assess the uptake of the recommendations and the barriers to effective implementation. An update of the 2013 guidelines is planned for 2015. Interim technical and programmatic updates may be developed if important new evidence becomes available.

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SECTION 5. THE USE OF CO-TRIMOXAZOLE PROPHYLAXIS FOR HIV-RELATED INFECTIONS AMONG ADULTS, ADOLESCENTS AND CHILDREN

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