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

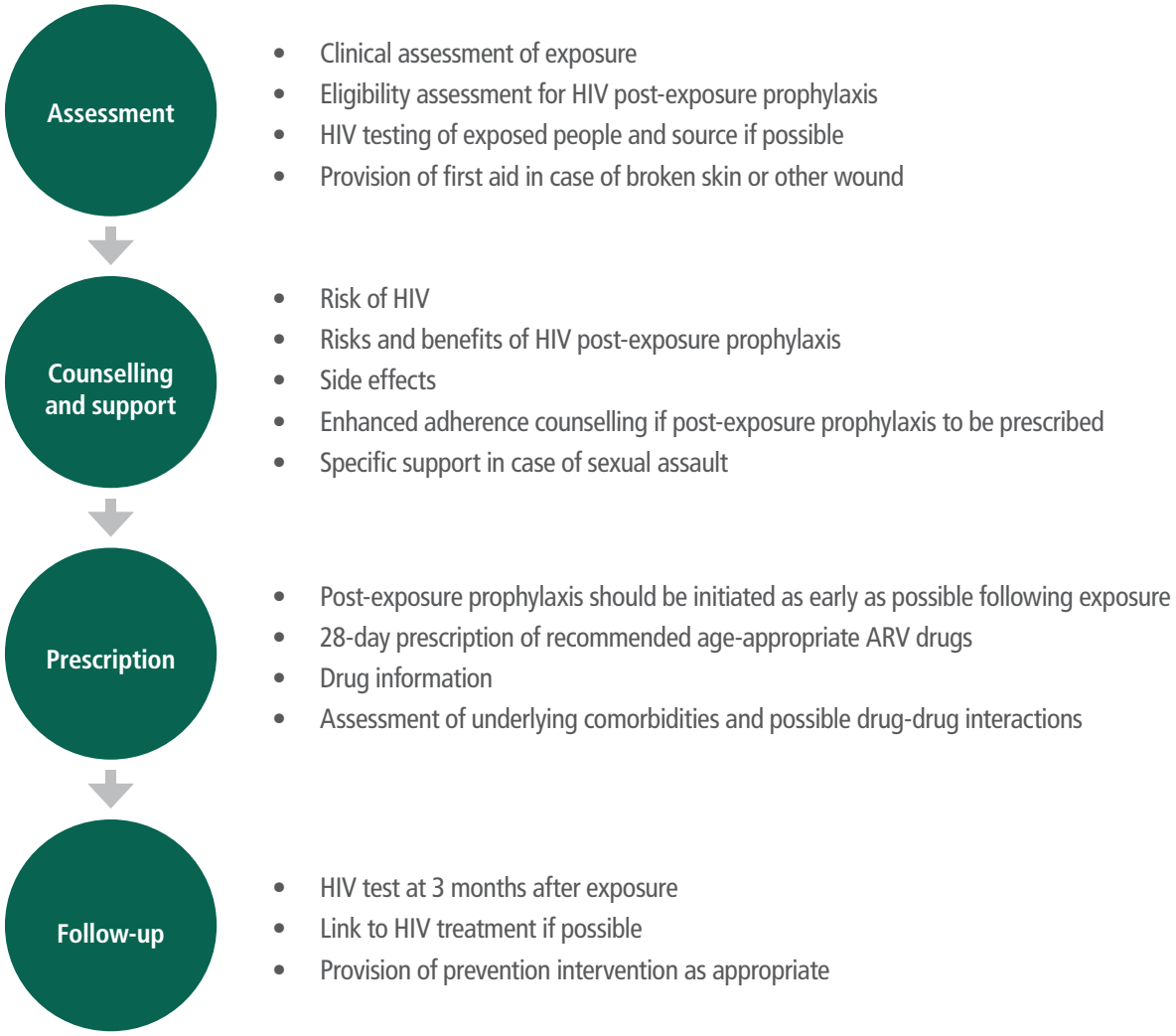
The clinical management guidance outlined in this section is intended for all individuals exposed to a potential HIV source. Subsection 4.11 gives additional guidance for specific populations.

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.