CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

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3 CLINICAL GUIDELINES: ANTIRETROVIRAL DRUGS FOR HIV PREVENTION

3.1 Oral pre-exposure prophylaxis for preventing the acquisition of HIV

NEW

Recommendation

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

Source: Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: World Health Organization; 2015 (http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en).

Background

Oral PrEP is the use of antiretroviral (ARV) drugs before HIV exposure by people who are not infected with HIV in order to block the acquisition of HIV.

Twelve trials on the effectiveness of oral PrEP have been conducted among serodiscordant couples, heterosexual men, women, men who have sex with men, people who inject drugs and transgender women *(1–12)*. Where adherence has been high, significant levels of efficacy have been achieved, showing the value of this intervention as part of combination prevention approaches.

In 2012, WHO recommended PrEP for use among serodiscordant couples, men who have sex with men and transgender people on the basis that demonstration projects were needed to ascertain optimal delivery approaches *(13)*. The 2013 *WHO Consolidated guidelines on the use of antiretroviral drugs in treating and preventing HIV infection* recommended PrEP in the context of demonstration projects. In 2014, WHO developed consolidated HIV guidelines for key populations, including men who have sex with men, people who inject drugs, sex workers, transgender people, and people in prisons and other closed settings *(14)*. In those guidelines, PrEP was strongly recommended for men who have sex with men.

This recommendation replaces previous WHO recommendations on PrEP and enables the offer of PrEP to be considered for people at substantial risk of acquiring HIV rather than limiting the recommendation to specific populations. Box 3.1 discusses the definition of "substantial risk". The new recommendation will enable a wider range of populations to benefit from this additional prevention option. It also allows the offer of PrEP to be

Box 3.1 Defining "substantial risk"

Substantial risk of HIV infection is provisionally defined as HIV incidence around 3 per 100 person-years or higher in the absence of PrEP. HIV incidence higher than 3 per 100 person-years has been identified among some groups of men who have sex with men, transgender women in many settings, and heterosexual men and women who have sexual partners with undiagnosed or untreated HIV infection. Individual risk varies within groups at substantial risk, depending on individual behaviour and the characteristics of sexual partners. Most of the PrEP trials reviewed for this recommendation identified and recruited groups at substantial risk of acquiring HIV, as demonstrated by the HIV incidence rate among participants in control arms that ranged between 3 and 9 per 100 person-years in most studies. Indeed, the HIV incidence in control arms of PrEP trials was often higher than anticipated, suggesting that PrEP attracts people at particularly high risk *(11)*. In locations where the overall incidence of HIV infection is low, there may be individuals at substantial risk who would be attracted to and benefit from PrEP services.

HIV incidence higher than 2 per 100 person-years was considered sufficient to warrant offering oral PrEP in the recommendations issued by the International Antiviral Society – USA expert panel in 2014 *(15)*. Thresholds for offering PrEP may vary depending on a variety of considerations, including epidemiological context or trends, available resources and the relative costs, feasibility and demand for PrEP.

Risk assessment tools for better defining substantial risk are being developed as part of WHO PrEP implementation guidance to be published in 2016.

based on local epidemiology and individual assessment, rather than risk group, and is intended to foster implementation that is informed by local information regarding the settings and circumstances of HIV transmission.

Rationale and supporting evidence

A systematic review and meta-analysis of PrEP trials containing TDF demonstrated that PrEP is effective in reducing the risk of acquiring HIV infection. The level of protection did not differ by age, sex, regimen (TDF versus FTC + TDF) and mode of acquiring HIV (rectal, penile or vaginal exposure) *(16)*. The level of protection was strongly correlated with adherence.

HIV infection

HIV infection was measured in 11 randomized controlled trials comparing PrEP to placebo; three randomized controlled trials comparing PrEP to no PrEP (such as delayed PrEP or "no pill") and three observational studies. A meta-analysis of data from 10 trials comparing PrEP with placebo demonstrated a 51% reduction in risk of HIV infection for PrEP versus placebo *(16–18)*.

Mode of acquisition

When studies were stratified by mode of acquisition (rectal, vaginal or penile exposure), PrEP showed similar effectiveness across groups. The relative risk of HIV infection for PrEP versus placebo for rectal exposure is 0.34 (95% CI: 0.15–0.80, $P = 0.01$). For penile or vaginal exposure, the relative risk of HIV infection for PrEP versus placebo is 0.54 (95% CI: 0.32–0.90, $P = 0.02$) *(16)*. Parenteral exposure to HIV was not analysed separately because only one study explicitly included people who inject drugs, and their exposure to HIV arose from sexual practices and incomplete access to sterile injection equipment.

Sex and gender

Of 10 randomized PrEP trials reporting HIV outcomes, women were included in six studies and men in seven studies. PrEP was effective for both men and women. The relative risk of HIV infection for PrEP versus placebo was 0.57 (95% CI 0.34–0.94; $P = 0.03$) among women and 0.38 (95% CI 0.20–0.60; $P = 0.0001$) among men. Two placebo-controlled trials that targeted women exclusively showed very low uptake of PrEP (less than one third) in the active arm and no effectiveness on an intent-to-treat basis *(7,10)*. The effectiveness of PrEP among women in four trials that included both women and men was higher. For example, among women younger than 30 years in a trial that included both men and women, the effectiveness was 72% (95% CI: 29–92%, $P = 0.01$) for TDF and 77% (95% CI: 25–90%, $P = 0.01$) for FTC + TDF PrEP *(4)*. The results from a recent study (HPTN 067) among young, predominantly single South African women receiving open-label FTC + TDF as PrEP showed that young women can maintain adherence, with 80% having substantial concentrations of detectable drug at week 4 and 65% at week 24 in the daily PrEP arm *(19)*. More information is needed about PrEP in transgender populations.

Adherence

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

When studies were stratified according to adherence levels (high, moderate and low based on the proportion in the active arms with detectable drug in blood), heterogeneity in effectiveness was greatly reduced within adherence subgroups, demonstrating that most heterogeneity between studies can be explained by differing adherence levels. Within adherence subgroups, PrEP is the most effective among the high-adherence group (defined as higher than 70% drug detection, but all studies in this group had adherence at or above 80%) and significantly reduces the risk of acquiring HIV in studies that had moderate levels of adherence (41–70% drug detection). Among studies with low adherence (40% or lower drug detection), PrEP shows no effect in reducing HIV infection *(16)*.

Safety

Ten randomized controlled trials comparing PrEP with placebo presented data on any adverse event. Across studies, the rates of any adverse event did not differ for PrEP versus placebo. Similarly, there was no statistical difference in rates of any adverse event

across subgroups, including mode of acquisition, adherence, sex, drug regimen, drug dosing or age *(16)*.

Eleven randomized controlled trials comparing PrEP with placebo presented the results for any grade 3 or 4 adverse event. Across studies, there was no statistical difference in the rates of any grade 3 or 4 adverse event for PrEP versus placebo, and there were no statistical differences across subgroup analyses, including adherence, sex, drug regimen, drug dosing or age *(16)*.

Several studies noted subclinical declines in renal functioning and bone mineral density among PrEP users *(20–22)*. These subclinical changes did not result in clinical events and were not progressive over time.

Drug resistance

The risk of drug resistance to FTC was low overall (11 people with FTC- or TDF-resistant HIV infection among 9222 PrEP users, or 0.1%), and this occurred mainly among people who were acutely infected with HIV when initiating PrEP: 7 people of the 11 with FTC- or TDF-resistant HIV infection among 9222 PrEP users. The proportion of people with drug-resistant HIV did not differ in the PrEP and placebo groups among everyone at risk, although the number of events was low ($n = 6$ people infected). Multiple HIV infections (8–50) were averted for every case of FTC resistance associated with starting PrEP in the presence of acute HIV infection *(16)*. Modelling the HIV drug resistance resulting from ART is predicted to far exceed that resulting from PrEP *(23)*. Although mathematical models inform the risk of resistance, their results rely on data from clinical trials and make assumptions about the risk of selection of drug-resistant virus during PrEP. How implementation of PrEP on a large scale affects resistance overall is unknown. Active surveillance during PrEP scale up may therefore be warranted.

Sexual and reproductive health outcomes

No evidence indicated that PrEP led to risk compensation in sexual practices, such as decreased condom use or more sexual partners *(24,25)*.

PrEP does not appear to affect the effectiveness of hormonal contraception, although two studies found trends towards higher rates of pregnancy among oral contraceptive users who also took PrEP. When multivariate analysis accounted for confounders, this relationship was not significant. Oral PrEP was not associated with increased adverse pregnancy-related events among women taking PrEP during early pregnancy *(4,10)*. More information is needed about interactions between PrEP and hormone therapy used by transgender people.

The systematic review sought to evaluate the effectiveness of PrEP in preventing HIV infection in the context of access to a combination of standard approaches to HIV prevention *(16)*. Across all trials, PrEP was provided in the context of a package of HIV prevention interventions, including regular HIV testing and counselling, provision of condoms, screening and treatment for sexually transmitted infections (STIs), adherence counselling and other options relevant to the study population, such as access to contraception for women and methadone maintenance therapy for people who inject opioids.

Cost and cost–effectiveness

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

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

A review of cost–effectiveness studies for PrEP found that, in generalized epidemics, giving priority for the use of PrEP to people at substantial risk of acquiring HIV infection increases impact *(26)*. Some of these studies found PrEP to be cost–effective within the context of ART expansion; others found no benefit. In concentrated epidemics (such as among men who have sex with men in the United States), PrEP could have a significant impact. Studies have found PrEP to be cost–effective, depending on the cost of the drug and delivery systems when PrEP uptake is higher among people at substantial risk. Higher PrEP uptake and adherence have been observed among men who have sex with men in demonstration projects *(2,27)*. The results vary widely depending on epidemic type, location and model parameters, including efficacy, cost, HIV incidence and target population *(28)*.

Equity and acceptability

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

PrEP acceptability has been reported in multiple populations, including women, serodiscordant couples, female sex workers, young women, people who inject drugs, transgender people and men who have sex with men. A qualitative literature review (131 peer-reviewed articles and 46 abstracts *(29)*) showed that individuals have substantial interest in accessing PrEP as an additional choice for HIV prevention. Population support for provision of PrEP was based on the knowledge of safety and effectiveness and the compatibility of PrEP with other prevention strategies.

Feasibility

Provision of oral PrEP to diverse populations has proven feasible in multiple trial settings and demonstration projects. Two placebo-controlled trials among women *(7,10)* found significant barriers to uptake and adherence, including the social stigma of being identified as living with HIV because of taking the medication, cultural barriers and lack of family or social support. However, programme settings differ from trials. PrEP adherence among women has been high when open-label PrEP is provided *(19,30)*.

The iPrEx OLE project and the Partners Demonstration Project both show that PrEP implementation is feasible for different populations, including men and women *(1,2)*. The PROUD study, conducted in the United Kingdom among men who have sex with men and designed to mimic real-life settings, demonstrated that PrEP is feasible and effective and is not associated with significant changes in behavioural risk *(11)*. Other PrEP demonstration projects in Botswana, South Africa, Thailand and the United States confirm that protective levels of adherence are feasible for most PrEP users *(19,30–34)*, although challenges remain to achieving high levels of adherence among young people *(34)*.

Implementation considerations

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

WHO will publish comprehensive implementation guidance for PrEP in 2016. The guidance will include practical suggestions for human resource utilization, laboratory monitoring, pharmacy services, drug procurement, counselling, communication, community engagement, coordination of services (including testing, treatment, PrEP, post-exposure prophylaxis (PEP) and other sexual and reproductive health services) and programme management. A number of implementation issues are addressed below.

Provider training

Health-care providers should be trained and supported so that they can explore sexual and injecting risk behaviour with people and help them consider their risk of acquiring HIV and the range of prevention options, including PrEP. This involves providing respectful and inclusive services, a familiarity with techniques for discussing sensitive behaviour and a strong patient–provider relationship that enables discussions of facilitators and barriers to engagement in health-care services, adherence and self-care. Service providers should be aware of the emotional and physical trauma that people at substantial risk of acquiring HIV infection may have experienced *(35)*. The capacity for respectful work with people who have experienced trauma involves communication and skills development. Services that are appropriate for young people – especially young women and key populations – are essential for the success of all HIV treatment and prevention programmes, including PrEP.

Involving communities

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

- Recognize the leadership and resilience of key populations in addressing the HIV epidemic at both the local and global levels and sustain their participation through adequate funding and support for community-based organizations.

- Ensure access to accurate knowledge and information about PrEP and early treatment by strengthening the capacity of community-based organizations in educating and training their communities about the use of PrEP.
- Promote and expand community-based services, especially services led by key populations.
- Ensure that PrEP is offered as a choice, free of coercion, and with access to other prevention strategies that may be preferred by individuals at substantial risk.
- Increase political commitment to rights, including the rights of key populations, by decriminalizing consensual sexual activity and gender expression.

Linking PrEP with other health and community services

People at substantial risk of acquiring HIV are often medically underserved, have few other effective HIV prevention options and frequently face social and legal challenges. Providing PrEP may give opportunities for increased access to a range of other health services and social support, including vaccinations for hepatitis B, reproductive and sexual health services (including managing STIs), mental health services, primary health care and legal services.

Community-based organizations – especially those working with key populations – should play a significant role in the roll-out of PrEP by engaging people at substantial risk, providing information about the availability and use of PrEP and promoting linkages between PrEP providers and other health, social and community support services.

PrEP as part of combination prevention

PrEP should always be provided together with other HIV prevention options. Harm-reduction interventions – including access to sterile or new injection materials – are the mainstay of preventing HIV transmission through unsafe injecting practices, and such supplies should be made available to anyone using injected substances or medications. Condoms and lubricants should be made available, including for sex workers, who should be empowered to insist on their use *(36)*.

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

HIV testing

HIV testing is required before PrEP is offered and regularly while PrEP is taken. People who test HIV negative but report high risk can be linked to prevention services where the potential for PrEP use can be assessed. HIV testing is required before PrEP is offered and should be conducted regularly (e.g. every three months) while PrEP is taken. The frequent HIV testing during PrEP use should also ideally become an opportunity for STI screening and management. Using quality-assured HIV testing is important, and using more sensitive tests has multiple advantages, including earlier HIV diagnosis and treatment, better counselling for people with acute HIV infection and minimizing the risk of drug resistance during PrEP and PEP. Rapid point-of-care third-generation HIV

antibody tests that use whole blood obtained by finger-prick or phlebotomy are available and are preferred to the use of oral fluids or second-generation tests when starting PrEP. Referral of people who test HIV positive to treatment services is essential.

Monitoring renal function

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

Hepatitis B

Hepatitis B virus (HBV) is endemic in many parts of the world where HIV is transmitted. The medications used for PrEP are active against HBV. Withdrawal of active therapy against HBV can lead to virological and clinical relapse. Clinical relapse did not occur during or after PrEP use in trials that included people with chronic HBV *(6,8)*. These trials excluded people with clinical liver cirrhosis and people with significant elevations in liver function tests. Testing PrEP users for hepatitis B surface antigen (HBsAg) is preferred. People with detectable HBsAg and alanine transaminase (ALT) elevated more than twice the upper limit of normal or clinical signs of cirrhosis could benefit from long-term therapy for HBV. Rapid point-of-care tests are available for HBsAg.

Adherence

Support for adherence should include information that PrEP is highly effective when used. Brief client-centred counselling that links daily medication use with a daily habit (such as waking up, going to sleep or a regular meal) may be helpful. Special programmes to facilitate adherence among particular groups – such as young people and women – may be needed. Support groups for PrEP users, including social media groups (for example, https://www.facebook.com/groups/PrEPFacts) may be helpful for peer-to-peer sharing of experience and challenges.

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

PrEP can be discontinued if a person taking PrEP is no longer at risk and when this situation is likely to be sustained. Engaging with community support groups is important to facilitate the recognition of circumstances that involve substantial risk of acquiring HIV. PrEP is only likely to be needed during periods of risk rather than for life. Such periods of risk may begin and end with changes in relationship status, alcohol and drug use, leaving school, leaving home, trauma, migration or other events *(37,38)*.

PrEP users should be advised that PrEP reaches protection after 7 doses *(39)*. Pharmacological studies suggest that full protection may require 4 doses for anal sex and 7 doses for vaginal sex *(39,40)*.

People who report exposure to HIV before full protection from PrEP has been achieved should be considered for PEP *(41)*. As with PEP, PrEP may be discontinued 28 days after the last potential exposure to HIV if people do not have continuing substantial risk for acquiring HIV.

Pregnancy

Pregnancy is associated with a higher risk of acquiring HIV, and HIV acquired during pregnancy or breastfeeding is associated with an increased risk of HIV transmission to the infant. In PrEP trials, exposure to TDF-containing PrEP during the first trimester of pregnancy was not associated with adverse pregnancy or infant outcomes. There is growing evidence of the safety of TDF and FTC + TDF during pregnancy and breastfeeding when used for treating maternal HIV or HBV *(42)*. Contraception services, safer conception management and links to antenatal care should be available when providing PrEP services for women. The risks and benefits of and alternatives to continuing to use PrEP during pregnancy and breastfeeding should be discussed with each person. Further research is needed to fully evaluate PrEP use during pregnancy and breastfeeding.

Research gaps

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

Severe long-term toxicity of TDF use for HIV treatment is rare. Surveillance of large-scale use of PrEP could identify rare but important clinical adverse events. For outcomes with few events (drug resistance and reproductive health outcomes), active surveillance during PrEP scale-up is warranted. Issues related to toxicity of TDF are addressed in section 4.6.3.

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

The IPERGAY trial showed high efficacy of PrEP dosing before and after sex among men who have sex with men who reported frequent sexual activity *(31)*. The HPTN 067 trial randomly compared recommendations for daily and non-daily PrEP regimens and found that the daily recommendation was associated with the highest concentrations of drug, the highest adherence and high coverage of sex events with pre- and post-exposure dosing among men who have sex with men in Bangkok and New York and women in Cape Town *(19,31,32)*. Medication requirements and use were also higher for those randomized to daily use. Daily dosing was the preferred choice for the majority of users. How best to adapt PrEP recommendations to diverse and changing sexual practices is an important focus for further implementation research.

PrEP costs are not limited to the cost of drugs and include costs for clinic staff, laboratory testing, pharmacy services, community education, provider education and monitoring and evaluation. Implementation research for minimizing costs should include evaluation of strategies that do not compromise the safety, effectiveness or quality of the information provided to prospective PrEP users. Lower prices for medications and laboratory tests could be achieved by purchasing at volume. PrEP is amendable to algorithmic care, which would enable task-sharing with less costly and more diverse personnel.

Research is needed to determine whether HIV status and renal function can be monitored less frequently without increasing the risk of adverse clinical outcomes. Optimal recommendations for starting and stopping PrEP to maximize use during periods of substantial risk would decrease medication requirements and increase the impact on HIV transmission.

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

3.2 Post-exposure prophylaxis

Background

The most recent WHO guideline on HIV PEP was published in December 2014 *(43)*. Recognizing the need to improve uptake and completion rates for PEP, the guideline does not differentiate between exposure sources but rather provides recommendations across all exposures. This section summarizes its main recommendations and clinical considerations. The full guideline includes more detailed information, including management of possible exposure to other conditions such as viral hepatitis, STIs, tetanus and pregnancy.

Assessing eligibility

HIV PEP should be offered and initiated as early as possible in all individuals with an exposure that has the potential for HIV transmission, preferably within 72 hours. For individuals who may not be able to access services within this time, providers should consider the range of essential interventions and referrals that should be offered to clients presenting after 72 hours.

Eligibility assessment should be based on the HIV status of the source whenever possible, and may include consideration of background prevalence and local epidemiological patterns.

Exposures that may warrant HIV PEP include the following:

- body fluids: blood, bloodstained saliva, breast milk, genital secretions and cerebrospinal, amniotic, peritoneal, synovial, pericardial or pleural fluid. While these

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).

Post-exposure prophylaxis ARV regimens for adults and adolescents:

- TDF + 3TC (or FTC) is recommended as the preferred backbone regimen[a] 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.

Post-exposure prophylaxis ARV regimens for children ≤10 years:

- AZT + 3TC is recommended as the preferred backbone regimen for HIV post-exposure prophylaxis for children aged 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 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.

Clinical considerations

NVP should not be used in children above the age of 2 years.

Prescribing practices

- A 28-day prescription of antiretroviral drugs should be provided for HIV post-exposure prophylaxis following initial risk assessment (strong recommendation, low-quality evidence).
- Enhanced adherence counselling[b] is suggested for individuals initiating HIV post-exposure prophylaxis (conditional recommendation, moderate-quality evidence).

[a] Backbone regimen refers to the two-NRTI component of an ART regimen (normally comprising of 3 ARV drugs).
[b] Enhanced adherence counselling includes baseline individual needs assessment, adherence counselling and education sessions and follow-up telephone calls.

Source: 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. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).

fluids carry a high risk of HIV infection, this list is not exhaustive. All cases should be assessed clinically, and health workers should make decisions as to whether the actual exposure constitutes a significant risk.

- types of exposure: 1) mucous membrane, i.e. sexual exposure; splashes to eye, nose, or oral cavity; and 2) parenteral.

Exposures that do not require HIV PEP include the following:

- when the exposed individual is already HIV positive;
- when the source is established to be HIV negative; and
- exposures to bodily fluids that do not pose a significant risk, i.e. tears, non-bloodstained saliva, urine and sweat.

In cases that do not require PEP, the exposed person should be counselled about limiting future exposure risk. Although HIV testing is not required, it may be provided if desired by the exposed person.

Clinical considerations

As with PrEP, there is concern about the potential risk of hepatic flares among people with chronic HBV once TDF-, 3TC- or FTC-based PEP is stopped. Assessment of HBV infection status should not be a precondition for offering TDF-, 3TC- or FTC-based PEP, but people with established chronic HBV infection should be monitored for hepatic flare after PEP discontinuation. Among people with unknown HBV status and where HBV testing is readily available, people started on TDF-, 3TC- or FTC-based PEP should be tested for HBV to detect active HBV infection and the need for ongoing HBV therapy after discontinuing PEP.

NVP should not be used for PEP for adults, adolescents and older children because of the risk of life-threatening serious adverse events associated with HIV-negative adults using this drug.

EFV is widely available as a third agent, as this drug is used as part of the preferred first-line ART regimen. EFV is well tolerated for treatment but has limited acceptability for use as PEP, as there are concerns about giving a drug associated with early neuropsychiatric adverse events to HIV-negative people who may have anxiety related to HIV exposure.

NVP has been widely used to prevent the transmission of HIV from mothers to HIV-uninfected infants and should be used for preterm babies or infants younger than two weeks of age where LPV/r oral liquid cannot be used. However, because the NVP toxicity profile beyond infancy remains unclear, its use should be avoided in children beyond the age of 2 years.

Full guidance on the management of other conditions associated with possible exposure to HIV is provided in the 2014 *Guidelines on post-exposure prophylaxis for HIV and the use of co-trimoxazole prophylaxis for HIV-related infections among adults, adolescents and children* (http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en).

3.3 Combination HIV prevention

Combination prevention programmes use a mix of biomedical, behavioural and structural interventions to meet the current HIV prevention needs of particular individuals and communities so as to have the greatest possible impact on reducing new infections. Well-designed combination prevention programmes are carefully tailored to national and local needs and conditions. They focus resources on the mix of programmatic and policy actions required to address both immediate risks and underlying vulnerability. They should be thoughtfully planned and managed to operate synergistically and consistently on multiple levels (e.g. individual, relationship, community and society) and over an adequate period of time. Combination prevention mobilizes communities, the private sector, governments and global resources in a collective undertaking. It requires and benefits from enhanced partnership and coordination and should incorporate mechanisms for learning, capacity building and flexibility to permit continual improvement and adaptation to the changing environment.

ARV drugs play a key role in HIV prevention. People taking ART who achieve optimal viral suppression are extremely unlikely to pass HIV to sexual partners. ARV drugs taken by people without HIV as PrEP or PEP are highly effective in preventing HIV acquisition.

Other **biomedical interventions** that reduce HIV risk practices and/or the probability of HIV transmission per contact event include the following:

- **Male and female condoms and condom compatible lubricant:** male condoms are estimated to reduce heterosexual transmission by at least 80% and to offer 64% protection in anal sex among men who have sex with men, if used consistently and correctly *(44,45)*. Fewer data are available for the efficacy of female condoms, but evidence suggests they can have a similar prevention effect *(46)*.
- **Needle and syringe programmes** are highly associated with a reduction in HIV transmission through injecting drug use *(47)*.
- **Opioid substitution therapy** with methadone or buprenorphine is the most effective form of treatment for opioid dependence and has the additional benefit of effectively reducing HIV risk behaviour and transmission through injecting drug use. Opioid substitution therapy also provides adherence support to people on ART *(48,49)*.
- **Voluntary medical male circumcision (VMMC):** three randomized clinical trials in Africa demonstrated an approximately 60% reduction in the risk of female-to-male sexual transmission *(50–52)*. For high-burden settings, WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended the inclusion of VMMC as an additional important strategy for presentation of heterosexually acquired HIV infection in men. Male circumcision should be offered as part of a comprehensive HIV prevention package, including safer sex education, providing and promoting condom use, providing HIV testing services (HTS) and linkage to care for those in need, and management of STIs. This intervention has reached over 10 million males in eastern and southern Africa *(53)*.

Behavioural interventions can reduce the frequency of potential transmission events, including the following:

- **Targeted information and education:** these are programmes that use various communication approaches, for example, school-based sex education, peer counselling and community-level and interpersonal counselling, including brief interventions to disseminate behavioural messages. These messages encourage people to reduce risk behaviour and increase behaviour that is protective (such as safer drug use, delaying sexual debut, reducing the frequency of unprotected sex with multiple partners, using male and female condoms correctly and consistently and knowing your HIV status and that of your partner). There is growing recognition that social media and mobile technology are important tools that can be integrated in HIV prevention programmes, and can be particularly critical in informing about and providing prevention services to populations such as men who have sex with men.
- **Structural and supportive interventions** may increase access to, uptake of and adherence to behavioural and biomedical interventions. Such interventions address the critical social, legal, political and environmental enablers that contribute to HIV transmission, including legal and policy reforms, measures to reduce stigma and discrimination (including in the health sector). In addition, they involve the promotion of gender and lesbian, gay, bisexual, transgender and intersex (LGBTI) equality and prevention of gender-based and LGBTI violence, economic empowerment, access to schooling and supportive interventions designed to enhance referrals, adherence, retention and community mobilization.

Combination prevention for key populations

WHO recommends a comprehensive package of evidence-based HIV-related recommendations for all key populations. The package comprises clinical interventions and a set of critical enablers required for successful implementation of programmes for the five key populations (Box 3.2).

Box 3.2 Comprehensive package of HIV prevention for key populations

a) Essential health sector interventions

1. Comprehensive condom and lubricant programming
2. Harm-reduction interventions for substance use (in particular, needle and syringe programmes, opioid substitution therapy and naloxone)
3. Behavioural interventions
4. HTS
5. HIV treatment and care
6. Prevention and management of coinfections and other comorbidities, including viral hepatitis, tuberculosis and mental health conditions
7. Sexual and reproductive health interventions

b) Essential strategies for an enabling environment

1. Supportive legislation, policy and financial commitment, including decriminalization of certain types of behaviour of key populations
2. Addressing stigma and discrimination, including by making health services available, accessible and acceptable
3. Community empowerment
4. Addressing violence against people from key populations

Source: Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/guidelines/keypopulations/en).

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