SUPPLEMENT ARTICLE

World Health Organization Guidelines on Postexposure Prophylaxis for HIV: Recommendations for a Public Health Approach

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The 2014 World Health Organization (WHO) guidelines for postexposure prophylaxis (PEP) developed recommendations for PEP irrespective of exposure source in recognition of the need to simplify eligibility assessment and prescribing practices. Traditionally, separate PEP guidelines have been developed according to exposure type, with difference guidelines for occupational exposure, nonoccupational exposure, and sexual assault. Recognizing the need to improve uptake and completion rates for PEP, the WHO 2014 guideline does not differentiate between exposure sources, but rather provides recommendations across all exposures. Recommendations for simplifying prescribing approaches and supporting adherence are also provided. In translating this guidance into national PEP guidelines, countries are encouraged to consider the need to provide PEP in a way that maximizes uptake and completion rates.

Keywords. HIV; guidelines; postexposure prophylaxis; World Health Organization.

In June 2014, the World Health Organization (WHO) convened an expert Guideline Review Group to review the evidence and formulate new recommendations for postexposure prophylaxis (PEP) for human immunodeficiency virus (HIV). Previous guidelines for HIV PEP issued by WHO in 2007 [1] were based on expert opinion and focused on HIV PEP for adults following occupational exposure and sexual assault; these guidelines recommended providing a 2- or 3-drug PEP regimen following the risk assessment of the exposure and the potential background drug resistance at population level. Antiretroviral (ARV) recommendations for HIV PEP followed WHO guidelines for antiretroviral therapy (ART) at that time [2].

The latest WHO guidelines, released in December 2014 [3], were developed based on a series of systematic evidence reviews and followed the methods of the Grading of Recommendations Assessment, Development and Evaluation, in which recommendations and their strength are formulated based on a formal assessment of the quality of the evidence [4]. In addition to assessing the quality of the evidence, the WHO guidelines development process considered additional elements of importance to end users such as values, preferences, feasibility, and cost.

The WHO 2014 PEP guidelines are based on the public health approach to delivering HIV services that seeks to ensure the widest possible access to high-quality services at a population level, aiming for a balance between best proven standard of care and feasibility [5]. In the case of PEP, the aim is to simplify prescribing and align regimens for PEP with those currently used for ART.

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sources, but rather provides recommendations across all exposures. Recommendations for simplifying prescribing approaches and supporting adherence are also provided.

This article summarizes the main recommendations of the 2014 WHO PEP guidelines, and provides references for key evidence reviews that underpin these recommendations.

ELIGIBILITY ASSESSMENT

Exposures Associated With HIV Risk

Estimates of HIV transmission risk per act vary among population groups and are difficult to interpret due to multiple confounding factors [6]. The estimated risk of HIV transmission via sexual exposures ranges from 4 per 10 000 exposures for condomless insertive penile-vaginal intercourse to 138 per 10 000 for condomless receptive anal intercourse [6]. The risk of percutaneous needle stick is in the range of 23 per 10 000 exposures to an infected source [6]. Various factors may affect the risk of transmission, including presence of other sexually transmitted infections, plasma and anogenital viral load of the source patient if known to be HIV-infected, and circumcision status [7].

Assessment of the Exposed Person's HIV Status

HIV PEP is not indicated if the exposed person is already HIV-infected. Individuals found to already be HIV-infected should be referred to appropriate services for eligibility assessment for ART according to national guidelines. Ruling out prior HIV infection is important because in some settings PEP comprises a 2-drug regimen, which if provided to HIV-infected individuals may lead to the development of drug resistance. In settings of lower prevalence, determination of exposure risk should be made on a case-by-case basis. Overall, only a small number of people (~1%) discontinue PEP because individuals considered at risk were subsequently found to be HIV-infected [8]. Nevertheless, HIV testing in the context of PEP should include initial testing of the exposed individual to identify those who may not benefit from PEP but could benefit from ART. If HIV testing is performed at the initial visit, a rapid test should be performed that can provide results within 2 hours, and often within 20 minutes. As in all other situations, HIV testing should be voluntary, and consent for HIV testing should be obtained with standard pretest and posttest counseling according to national and local protocols. Where the individual has limited or no capacity to consent (most commonly children), a parent or guardian can provide consent. Risks and benefits of testing should be sufficiently explained to the child and parent/guardian so that an informed decision can be made. However, assessment of HIV status of the exposed individual should not be a barrier to initiating PEP. In emergency situations where HIV testing and counseling is not readily available but the potential HIV risk is high, or if the exposed person refuses initial testing, PEP should be initiated and HIV testing and counseling undertaken as soon as possible.

Assessment of the Source's HIV Status

Determination of the HIV status 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. According to published studies, around 9% of individuals starting PEP are subsequently discontinued because the source case is subsequently considered to have low or no risk of transmitting HIV [8]. However, ascertainment of source HIV status may be difficult in some settings (eg, sexual assault), and PEP initiation should never be delayed by the availability of the source's HIV test results. In settings with generalized HIV epidemics and those among key affected populations with high infection burden (eg, men who have sex with men, injection drug users, sex workers), it is reasonable to assume that all sources of unknown HIV status pose a risk of infection. If the source is determined to be HIV-infected, provision should be made to link them to appropriate treatment and care. If the source is established to be HIV negative, PEP should be discontinued.

Best-practice guidance for PEP eligibility assessment is summarized in Table 1.

Table 1. Practical Guidance for Assessing Postexposure Prophylaxis 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, and ideally within 72 hours.[a]
- 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.[b]
- Exposures that may warrant HIV PEP include:
  - Bodily fluids: blood, blood-stained saliva, breast milk, genital secretions; cerebrospinal, amniotic, peritoneal, synovial, pericardial, or pleural fluids.
  - Mucous membrane: sexual exposure; splashes to eye, nose, or oral cavity.
  - Parenteral exposures.
- Exposures that do not require HIV PEP include:
  - When the exposed individual is HIV already positive.
  - When the source is established to be HIV negative.
  - Exposures to bodily fluids that do not pose a significant risk, ie, tears, non-blood-stained saliva, urine, and sweat.

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

Abbreviations: HIV, human immunodeficiency virus; PEP, postexposure prophylaxis.

[a] Although PEP is ideally provided within 72 hours of exposure, there may be instances when patients are unable to access services within this timeframe. Providers should consider the range of other essential interventions and referrals that should be offered to clients presenting after the 72-hour period.

[b] In some settings with high HIV prevalence or where the source is known to be at high risk for HIV infection, all exposures may be considered for PEP without a risk assessment.

PEP REGIMENS AND PRESCRIBING PRACTICES

Previously, PEP guidelines recommended different PEP regimens for different circumstances, with 2 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 [1]. More recent national guidelines have shifted toward recommending a 3-drug regimen for all, given the availability of less toxic and better tolerated medications and considering the difficulty in evaluating the risk of drug resistance and need to simplify prescribing [9]. Providing 3 drugs for HIV PEP is also consistent with recommendations for treatment, the standard for which is triple-combination therapy. Although the addition of a third drug increases expense and the potential for drug-related toxicity, reported PEP completion rates are similar comparing 2- and 3-drug regimens [8].

There may be situations where only 2-drug regimens are available for PEP, or where the risk of additional toxicity outweighs the benefit. This is an acceptable option, supported by evidence from animal studies with PEP [10] as well as other ARV-based prevention interventions, including prevention of mother-to-child transmission [11] and preexposure prophylaxis [12].

Recommendations for preferred drug regimens for adults and children are summarized in Table 2. These recommendations are based on systematic reviews of adverse drug reactions and completion rates associated with different PEP drugs in adults [13] and children [14], together with considerations of drug cost and availability in resource-limited settings [15].

The new WHO guidelines also provide recommendations for PEP prescribing and adherence support. Prompt PEP initiation (within 72 hours postexposure, but the sooner, the better) and completion of the full 28-day course of ARV drugs for HIV PEP are thought to be required to maximize the benefit of the intervention. Prescribing practices vary in the methods of dispensing ARV drugs following initial risk assessment. Partial prescriptions, often referred to as "starter packs," consist of an initial supply of drugs and have been used as a way to ensure that final serostatus determination and counseling could be completed prior to the wider use of rapid testing techniques. Although dispensing of a partial prescription is still used in many settings to facilitate rapid initiation of PEP by nonspecialist healthcare professionals, the current ART regimens are sufficiently well-tolerated that all healthcare professionals should be able to initiate and dispense the full 28-day course of ARVs for PEP, and monitor patients for uncommon side effects.

Evidence from a systematic review conducted to inform the guideline process suggested that acceptance and completion rates are better among people given a full 28-day course of PEP compared to those provided with a starter pack [16].

Table 2. Recommended Regimens for Postexposure Prophylaxis for Adults, Adolescents, and Children

Number of antiretroviral drugs: • A 2-drug PEP regimen is effective, but 3 drugs are preferred. (Conditional recommendation, low quality of evidence)
Preferred antiretroviral regimen for adults and adolescents: • TDF + 3TC (or FTC) is recommended as the preferred backbone regimen for HIV PEP in adults and adolescents. (Strong recommendation, low-to-moderate quality of evidence) • LPV/r or ATV/r are suggested as the preferred third drug for HIV PEP in adults and adolescents. Where available, RAL, DRV/r, or EFV can be considered as alternative options. (Conditional recommendation, very low quality of evidence)
Preferred antiretroviral regimen for children ≤10 y: • ZDV + 3TC is recommended as the preferred backbone for HIV PEP in children aged ≤10 y. 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 PEP in children aged ≤10 y. An age-appropriate alternative regimen can be identified among ATV/r, RAL, DRV, EFV, and NVP. (Conditional recommendation, very low quality of evidence)
Prescribing frequency: • A full 28-day prescription of antiretrovirals should be provided for HIV PEP following initial risk assessment. (Strong recommendation, very low quality of evidence)
Adherence support: • Enhanced adherence counseling is suggested for all individuals initiating HIV PEP. (Conditional recommendation, moderate quality of evidence)

Abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; HIV, human immunodeficiency virus; LPV, lopinavir; NVP, nevirapine; PEP, postexposure prophylaxis; /r, boosted with ritonavir; RAL, raltegravir; TDF, tenofovir; ZDV, zidovudine.

Prescribing the full course at the initial assessment could be considered less resource intensive, as in the majority of cases it may negate the need for a follow-up appointment [16]. The guideline development group considered that provision of a partial prescription with the necessity to return for follow-up appointments could increase inequity in populations with limited access to healthcare facilities. It was therefore recommended that a full 28-day prescription of ARVs should be provided for HIV PEP following initial risk assessment; this is a strong recommendation, but based on very low quality of evidence.

Finally, recognizing the poor completion rates for PEP, and considering the evidence that enhanced adherence support may benefit adherence, the WHO 2014 PEP guidelines recommend that enhanced adherence support be offered as part of PEP; this is a conditional recommendation based on moderate-quality evidence. Providing enhanced counseling was considered to be potentially more resource intensive, including costs to train staff and monitoring of outcomes, and to possibly require increased time; however, current PEP completion rates are low in almost all settings, and there is a need to consider specific interventions to improve outcomes. As with routine

counseling, the availability of adherence counseling should not delay PEP initiation. Health workers who are already involved in adherence counseling and patient education could support this task. The committee identified this area as one in need of further research, to define the optimally efficient and effective ways to provide PEP adherence counseling.

CONCLUSIONS

The 2014 WHO PEP guidelines developed recommendations for PEP irrespective of exposure source in recognition of the need to simplify eligibility assessment and prescribing practices. In translating this guidance into national PEP guidelines, countries are encouraged to consider the need to provide PEP in a way that maximizes uptake and completion rates.

Notes

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References

1. Post-exposure prophylaxis to prevent HIV infection. Joint WHO/ILO guidelines on post-exposure prophylaxis (PEP) to prevent HIV infection. Geneva, Switzerland: WHO, **2007**.
2. Guidelines Review Committee, World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents recommendations for a public health approach. Geneva, Switzerland: WHO, **2006**.
3. World Health Organization. Guidelines on post exposure prophylaxis for HIV. Recommendations for a public health approach. Geneva, Switzerland: WHO, **2014**.
4. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ **2008**; 336:995–8.
5. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: WHO, **2013**.
6. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS **2014**; 28:1509–19.
7. Benn P, Fisher M, Kulasegaram R; BASHH; PEPSE Guidelines Writing Group Clinical Effectiveness Group. UK guideline for the use of post-exposure prophylaxis for HIV following sexual exposure (2011). Int J STD AIDS **2011**; 22:695–708.
8. Ford N, Irvine C, Shubber Z, et al. Adherence to HIV post-exposure prophylaxis: a systematic review and meta-analysis. AIDS **2014**; 28:2721–7.
9. Kuhar DT, Henderson DK, Struble KA, et al. Updated US Public Health Service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. Infect Control Hosp Epidemiol **2013**; 34:875–92.
10. Irvine C, Egan KJ, Shubber Z, Van Rompay KKA, Beanland RL, Ford N. Efficacy of HIV postexposure prophylaxis: systematic review and meta-analysis of nonhuman primate studies. Clin Infect Dis **2015**; 60(suppl 3): S165–9.
11. Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. Cochrane Database Syst Rev **2011**:CD003510.
12. Okwundu CI, Uthman OA, Okoromah CA. Antiretroviral pre-exposure prophylaxis (PrEP) for preventing HIV in high-risk individuals. Cochrane Database Syst Rev **2012**; 7:CD007189.
13. Ford N, Shubber Z, Calmy A, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. Clin Infect Dis **2015**; 60(suppl 3):S170–6.
14. Penazzato M, Dominguez K, Cotton M, Barlow-Mosha L, Ford N. Choice of antiretroviral drugs for postexposure prophylaxis for children: a systematic review. Clin Infect Dis **2015**; 60(suppl 3):S177–81.
15. Beanland RL, Irvine CM, Green K. End users' views and preferences on prescribing and taking postexposure prophylaxis for prevention of HIV: methods to support World Health Organization guideline development. Clin Infect Dis **2015**; 60(suppl 3):S191–5.
16. Ford N, Venter F, Irvine C, Beanland RL, Shubber Z. Starter packs versus full prescription of antiretroviral drugs for postexposure prophylaxis: a systematic review. Clin Infect Dis **2015**; 60(suppl 3):S182–6.