Postexposure Prophylaxis Against Human Immunodeficiency Virus (HIV): New Guidelines From the WHO: A Perspective

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RATIONALE FOR PEP AND NEW GUIDELINES

Guidelines for antiretroviral (ARV) prophylaxis following high-risk exposure (postexposure prophylaxis—PEP) to human immunodeficiency virus (HIV) date to 1990, when the US Centers for Disease Control and Prevention (CDC) first considered such recommendations for persons with occupational exposures to HIV [1]. The US Public Health Service also issued recommendations focused on occupational exposures in 1996 [2]; these recommendations have been updated 5 times [3–7]. Prophylaxis after non-occupational exposures to HIV (via sexual contact and sharing of drug-using paraphernalia) was first addressed by the CDC in 1998 [8] and updated in 2005 [9]. The World Health Organization (WHO) first considered PEP in 2007 and included PEP recommendations in the 2013 consolidated guidelines; both documents focused on occupational exposures [10, 11]. The most recently published WHO guidelines on PEP recommend that a PEP regimen be administered as soon as possible within the 72-hour window period after an HIV-related exposure and that whereas a 2-drug antiretroviral regimen is acceptable, a 3-drug regimen is preferred [12].

The most recent WHO guidelines differ from earlier recommendations in that PEP for both occupational and nonoccupational exposures are considered in the same document [12]. This approach is a welcome step in addressing this topic in resource-limited settings (RLS) for two main reasons: (1) WHO HIV treatment recommendations have been successful in the past 2 decades in great part because of their simplified approach, making them practical to communicate and to implement in RLS; this unified approach to PEP is consistent with that approach; and (2) the ARV regimens used for PEP, which have changed greatly over the years, and the procedures for monitoring persons on PEP are the same for both types of exposures; hence it is logical to combine recommendations for occupational and nonoccupational PEP in one document.

Development of PEP guidelines has raised important scientific and implementation issues since they were first developed in 1990; these include efficacy of PEP, choice of ARV regimens, and practical issues of implementation, including follow-up of persons taking PEP [1]. These issues are all highly relevant for implementation of PEP in RLS.

EVIDENCE SUPPORTING PEP

In general, although the evidence supporting the use of PEP for the prevention of HIV infection is limited, PEP has come to be accepted as a standard of care in the medical community for the prevention of HIV infection after isolated exposures. The strongest evidence supporting the use of PEP is based on a case-control study among hospital workers documenting that prompt initiation of zidovudine (AZT) after a hospital-associated occupational exposure was associated with an 81% decrease in the risk for acquiring HIV.
Although the initial case-control study among hospital workers involved the use of AZT alone, subsequent observational studies in children and adults have documented the use of 2-drug and 3-drug regimens for PEP in both occupational and nonoccupational settings. Observational PEP studies to date have shown better adherence for 2-drug regimens compared to 3-drug regimens and for once-a-day regimens compared to regimens administered more than once a day [19, 20]. Among those receiving 3-drug regimens, fewer side effects and better completion rates have been observed for integrase-based compared to protease inhibitor-based regimens [19, 20]. In general, nonnucleoside reverse transcriptase inhibitor-based 3-drug regimens have been avoided because of the risk of liver toxicity in persons receiving nevirapine (NVP), and of neuropsychiatric adverse effects in those receiving efavirenz (EFV) [9, 21, 22]. Studies of ARVs as treatment for established HIV treatment in adults and children indicate that 3-drug ARV regimens result in better virologic suppression compared to 2-drug regimens, suggesting theoretically greater benefit of 3-drug regimens for PEP [23]. Because no PEP studies have compared the efficacy of 2-drug vs. 3-drug regimens, and because the current WHO guidelines target RLS, the premise of “two ARVs are acceptable, but three ARVs are preferred” was recommended by WHO to allow for flexibility of regimen choices in the context of limited data. The guidelines note the theoretical benefit of a 3-drug regimen in the setting of exposure to a drug-resistant strain of HIV; they also acknowledge that use of a 3-drug regimen would be consistent with the current ARV treatment regimens. They suggest that the use of 2-drug regimens be limited to situations where the risks of additional toxicity outweigh the potential benefit. However, making these types of assessments may be difficult in RLS—hopefully not resulting in delays in initiating PEP. Countries may wish to standardize recommendations within their countries by supporting 3-drug regimens, which would be consistent with ARV treatment practices.

**CHOICE OF PEP REGIMENS**

Much attention is given in the Guidelines to the specific choices of ARV drugs in 2- or 3-drug regimens. The Guidelines recommend the use of a tenofovir and lamivudine (or emtricitabine) (TDF+3TC (or FTC)) backbone with lopinavir/ritonavir (LPV/r) or atazanavir/ritonavir (ATV/r) as the third drug. The alternatives for the third drug, where available, are raltegravir (RAL), darunavir/ritonavir (DRV/r), and EFV. Of these, EFV is widely available and less costly than the other drugs. However, potential concerns have been raised about the use of a drug associated with early neuropsychiatric events (EFV) in HIV-negative individuals who may have anxiety related to their HIV exposure. A recent study reported high rates of discontinuation associated with EFV when used in PEP, suggesting alternatives may be preferred [24].

Other clinical considerations are discussed, including concerns about the potential for renal toxicity with TDF and for hepatic flares on discontinuation of the drug in those with hepatitis B infection. More information is needed on these issues. If TDF is not tolerated or is contraindicated, a backbone of AZT+3TC can be used. This alternative backbone is also often readily available.

There is a need for more studies of head-to-head comparisons of completion rates and tolerability of PEP regimens including with newer drugs such as various integrase inhibitor-based regimens (ie, RAL vs dolutegravir or elvitegravir) and studies of head-to-head comparisons on tissue penetration of various ARV drugs using the same methodology [25]. Such studies of tissue penetration may help inform the next generation of PEP recommendations.

Recommendations for pediatric regimens (<10 years) are for the use of AZT+3TC as the preferred backbone, with abacavir (ABC)+3TC or TDF+3TC (or FTC) as alternatives. LPV/r is recommended as the third drug with ATV/r, RAL, or NVP (if younger than 3 years) and EFV or DRV/r (if 3 years and older) as alternatives. The problems with the availability and/or cost of ATV/r, RAL, and DRV/r are still impediments for their use. There is a need for more tolerable and effective PEP regimen choices for children, particularly in the first 2 years of life.

The Guidelines discuss the use of partial vs full prescriptions of the ARVs for PEP and conclude that a full 28-day prescription is preferred. This removes the requirement for exposed persons to return to obtain more drugs after 1 week and will hopefully increase the likelihood that they will complete the full 28 days of prophylaxis. The drugs are also commonly packaged as 1-month supplies, which facilitates dispensing without the need to repackage.

**PEP IMPLEMENTATION IN RESOURCE-LIMITED SETTINGS**

Writing guidelines is one thing; implementing them in RLS is another. The guidelines represent a welcome step in the
simplification and harmonization of PEP guidelines in this context. To date, PEP guidelines have consisted of stepwise algorithms involving complex risk assessments and differing interventions. Harmonizing PEP regimens with the WHO-recommended antiretroviral therapy (ART) regimens is a huge step in ensuring that ART providers are able to prescribe PEP easily and to provide HIV-exposed individuals with a full course of ARVs for PEP at the time an exposure is reported. By eliminating the parallel forecasting, logistics, procurement, and reporting burden that the previous PEP recommendations imposed upon already strained health systems, health-care workers (HCWs) can focus instead on strengthening awareness around the availability of PEP, creating demand for PEP services, and putting systems in place that maximize the likelihood that HIV-exposed individuals who begin PEP will adhere to their regimens and complete the entire 28-day course. WHO’s inclusion of pediatric PEP in the updated guidelines was a critical addition, as there has been considerable confusion as to how to administer PEP appropriately for children.

Occupational PEP is a powerful prevention intervention that is grossly underutilized in RLS. The relative dearth of occupational health clinics where HCWs can seek services is an obstacle to HCW uptake of occupational PEP services. Additionally, the rapid decentralization of services accompanied by the significant amount of task shifting that has taken place in RLS has created a large number of HCWs neither properly trained to identify risk exposures nor to act appropriately when they occur, even when those services are available. An oft-forget segment of the health workforce that is at high risk for occupational exposure, yet frequently has little training regarding the exposures that qualify for PEP and/or the availability of PEP interventions, are students and recent graduates in internships or doing field work. Additionally, in light of the evidence regarding loss to follow-up associated with referrals, many countries are grappling with the challenge of how to provide occupational PEP in facilities, such as peripheral health centers, that may not offer ART.

Uptake of nonoccupational PEP services faces a significant number of structural, cultural, geographic, and demographic barriers in RLS. The 2014 Joint United Nations Programme on HIV/AIDS GAP report stated that up to 45% of adolescent women (aged 15–19) in RLS experience some form of sexual violence [26]. Knowledge of PEP, including its presumed efficacy and the importance of starting PEP early, is very low in places where HIV prevalence is highest. This could be addressed by integrating PEP messages into educational interventions and prevention messaging targeting in- and out-of-school youth, as well as into the broader prevention messaging in high-prevalence countries. There should be clear messages about where ARVs for PEP can be obtained, the indications for PEP, the efficacy of PEP, and the importance of early presentation after a nonoccupational exposure to HIV.

Most evaluations following a nonoccupational exposure are conducted by nonphysician HCWs. Governments should authorize nurses and clinical officers to prescribe ARVs for PEP to maximize initiation of PEP and to minimize the impact of providing PEP on already-burdened HIV treatment facilities. Additionally, there should be clear guidance as to how ministries of health should engage with law enforcement and the criminal justice system around PEP to maximize health-seeking behavior in victims of sexual assault. Because many victims of sexual violence are children or adolescents, legal issues related to consent for testing and treatment must be addressed in order to ensure that victims’ rights are protected and respected regardless of their age.

Persons with nonoccupational HIV exposures will require additional services such as screening and treatment for other sexually transmitted infections (STIs) and treatment for drug addiction disorders. Appropriate and timely referrals for such services should be available, including for persons who appear to be at risk for ongoing high-risk exposures to HIV.

For both occupational and nonoccupational PEP service provision, a 1-stop model should be the norm to avoid losing exposed individuals in the shuffle from one clinical service department to another. All health facilities offering PEP should have a designated counselor who is available at all times. It might also be useful to consider a case management model of support to prevent attrition and enhance follow-up of HIV-exposed individuals. Strategies such as short message service phone reminders and community health workers/treatment supporters could be used to maintain contact with exposed individuals beyond the 28-day ARV period to enhance appropriate follow-up testing, given that the losses after PEP administration are significant.

It is the hope of the WHO, and of HCWs around the world, that the publication of the WHO PEP guidelines will make PEP more widely available in RLS. Although the prevention of exposures to HIV, whether occupational, sexual, or by sharing of drug-using paraphernalia, remains the mainstay of prevention of transmission of HIV in these circumstances, availability of PEP will provide a health benefit to those who require PEP and will contribute to HIV prevention programs in RLS.

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