The Transition From Postexposure Prophylaxis to Preexposure Prophylaxis: An Emerging Opportunity for Biobehavioral HIV Prevention

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Although some individuals who present for antiretroviral postexposure prophylaxis (PEP) had a 1-time exposure to human immunodeficiency virus (HIV), others may be recurrently risky. Given that preexposure prophylaxis (PrEP) has been shown to be efficacious, identification of those individuals who present for PEP who might benefit from PrEP is important to decrease HIV acquisition in high-risk individuals. While inclusion criteria for PrEP have been developed, there is a paucity of data to help clinicians determine which PEP users are at highest risk for HIV acquisition and therefore should be offered PrEP. We will discuss the rationale for using PrEP after PEP use, and will focus on the assessment of PEP users who may benefit from PrEP.

Keywords. HIV prevention; preexposure prophylaxis; postexposure prophylaxis.

The human immunodeficiency virus (HIV) epidemic continues to persist globally, with 2.3 million new infections in 2012 [1]. In light of ongoing challenges to develop an HIV vaccine and limited efficacy of traditional approaches to HIV prevention, several methods of biomedical prevention have been conceived and studied in the past 2 decades that offer a novel paradigm to stem the HIV epidemic. HIV postexposure prophylaxis (PEP) is the use of 28 days of antiretroviral medication begun within 72 hours after a sexual or parenteral exposure to HIV, whereas preexposure prophylaxis (PrEP) involves daily or intermittent dosing of antiretroviral medication over an extended period of time in anticipation of 1 or more high-risk exposures to HIV. Both approaches are biobehavioral interventions as perceptions of risk, medication adherence, and risk compensation are mediated by social and behavioral factors that can facilitate or impede optimal outcomes after these interventions are deployed. The use of PrEP has been shown to reduce HIV transmission in high-risk populations in several large, multisite, randomized trials, with medication adherence being the major predictor of PrEP efficacy [2–7]. The use of PEP is based on a case-control study of HIV infection among patients with occupational exposures and animal studies [8, 9]. Performing a randomized, placebo-controlled trials demonstrating the benefit of PEP is neither feasible nor ethical, which limits the ability to estimate the number needed to treat on a national or international scale. Certainly, each person newly infected with HIV could have theoretically been a candidate for PEP after the defining exposure that led to HIV infection. However, PEP awareness and provision may be highly variable in different settings. Despite the fact that normative bodies have recommended PEP for >15 years [10], there are limited clinical and behavioral outcome data for individuals who present for PEP.

Several studies suggest that some patients receiving PEP remain at increased risk for future HIV acquisition. A survey of HIV-uninfected PEP users between 2001 and 2010 observed that Australian men who have sex with men (MSM) who were PEP users were likely to have a long-term HIV-infected partner, multiple sex partners, and/or engage in anal sex with casual partners compared with MSM who did not use PEP [11]. Two
other Australian studies reported an HIV incidence to be 1.27 per 100 person-years among PEP users [12] and a hazard ratio of 2.67 for HIV seroconversion in MSM who used PEP vs MSM who did not use PEP [13]. A Brazilian study noted an HIV incidence of 2.9 per 100 person-years among 200 MSM who had access to, and education about, HIV PEP [14]. An Amsterdam cohort had an HIV incidence of 6.4 per 100 person-years among MSM who used PEP between 2000 and 2009 [15]. A Boston-based study reported rising PEP utilization and frequent PEP recurrence [16] with an HIV incidence of 2.2 per 100 person-years among PEP-using MSM between 1997 and 2013 [17]. These data suggest that the PEP encounter should be viewed as a prevention opportunity to help at-risk persons who are acutely seeking PEP to engage in a sustained program of risk reduction, which may include counseling and referral to behavioral health and substance use treatment services and consideration of HIV PrEP.

**RATIONALE FOR PEP TO PREP TRANSITION**

By definition, people who present for PEP have sustained a high-risk exposure to HIV. It is imperative that providers determine the reasons for the risk, and if it is ongoing, they should consider whether the person would benefit from PrEP. Most patients who present for PEP are given a 2- or 3-drug antiretroviral regimen containing tenofovir and emtricitabine [18]. Given that the only regimen currently approved for PrEP by the US Food and Drug Administration is tenofovir-emtricitabine [19], patients who tolerate a 28-day course of a PEP regimen containing this combination of medications would presumably also tolerate the same medications for PrEP. Conversely, some patients who have problems tolerating or adhering to tenofovir-based regimens may encounter similar challenges with PrEP, although the side effects may primarily be due to the third drug in the PEP regimen (eg, a ritonavir-boosted protease inhibitor). Before initiating PrEP assessment, comorbid mental illness and recreational substance use that may hinder adherence to PrEP should be preemptively addressed. Given that the standard of most PEP protocols involves multiple visits with a single provider within a short time interval, there are several opportunities to reinforce sexual risk reduction messages, which have been shown to be effective, especially when administered in a more intensive and structured manner [20].

PEP and PrEP are not merely biomedical interventions, as prevention of HIV or other sexually transmitted infections (STIs) entails combining the provision of medication with counseling to promote medication adherence, as well as risk reduction counseling. Ongoing communication with HIV-infected African patients through text messaging [21] and home visits for PrEP patients [22] have been associated with improved clinical outcomes. Patients who have attended all scheduled PEP visits and who may have also received additional behavioral or adherence counseling who indicate that they may continue to engage in HIV risk-related behaviors should be evaluated to transition to PrEP.

**WHICH PEP PATIENTS SHOULD BE REFERRED FOR PREP?**

The US Public Health Service recommends PrEP for MSM, heterosexual men and women, and injection drug users who are at “substantial risk for HIV acquisition” [23]. Sexual risk is defined as having an HIV-infected sex partner, a recent STI, multiple sex partners, inconsistent or no condom use, and/or engaging in transactional sex work. Although these criteria may apply to some PEP users, additional assessment should be done. Patients who present recurrently for PEP may be thought to be prime candidates for PrEP; however, some studies have not demonstrated a significant association with recurrent PEP use and HIV acquisition [12, 17]. It may be more important for clinicians to discuss anticipated risk behavior when a person completes a PEP course, rather than assuming that recurrent PEP use would make a patient ready to initiate PrEP, which is a chronic commitment. Studies are under way to assess whether PrEP would be particularly acceptable for populations particularly affected by HIV, such as young black MSM [24]. Retrospective data from a single center in Boston demonstrated that young, black, and Latino MSM were significantly associated with future HIV infection among PEP patients [17], which mirrors groups identified by Centers for Disease Control and Prevention (CDC) surveillance data for incident HIV infections [25]. Additional longitudinal data for PEP patients will aid in identifying specific high-risk groups for HIV acquisition.

The type of sexual contact also impacts the cumulative risk of HIV acquisition over time [26]. For example, someone who presents for PEP after condomless receptive anal intercourse with exposure to the ejaculate of an HIV-infected partner who was not on treatment is at far greater risk of HIV acquisition than someone who is the insertive partner who presents after condom malfunction with an HIV-infected partner on antiretroviral therapy. In addition to assessing sexual behaviors, it is important to determine patterns of substance use during sex, as individuals who engage in sex while under the influence of substances may need PrEP even though they may not often engage in condomless sex but may be at risk for PrEP nonadherence, given that they may be less likely to negotiate condom use when engaging in sex.

Because PrEP will only be effective if individuals are adherent, if a PEP user with ongoing HIV risk does not wish to transition to PrEP, efforts should be made to continue to engage him or her in medical care and offer supportive services...
WHEN IS IT SAFE TO START PREP AFTER PEP?

The 2005 CDC PEP guidelines recommend a 6-month HIV testing protocol before determining that a patient who has presented for PEP is not HIV infected [27]. After the introduction of more-sensitive assays, the US Public Health Service and New York AIDS Institute recommended that the follow-up period for HIV testing need not exceed 4 months after the initial exposure that led to PEP use, if a fourth-generation antigen-antibody assay is employed [28, 29]. Several studies have demonstrated that some individuals may continue to engage in high-risk sexual behavior despite being observed for HIV infection while using PEP [13, 15], which may engender a sense of urgency for a transition to PrEP after a 28-day PEP course. The most recent US Public Health Service PrEP guidelines suggest that patients with a negative HIV antibody test without signs or symptoms of acute retroviral syndrome in the preceding 4 weeks can be considered HIV uninfected and eligible for PrEP [23]. However, because some patients may not manifest classic symptoms of acute retroviral syndrome, it is possible that these criteria may not identify all patients who may be in the window period for acute HIV infection [30], particularly for those who have recently completed a 28-day course of antiretroviral medications for PEP, as this may delay such symptoms and HIV seroconversion. In the ideal circumstance, it may be prudent to wait 4 weeks or longer to monitor PEP users for acute HIV infection before initiating PrEP. However, for patients who continue to have high-risk exposures during the observation period, early transition to PrEP may be preferable. Although routinely obtaining a plasma HIV RNA test prior to PrEP initiation has not been endorsed by normative bodies due to the risk of a false-positive or false-negative test, the use of this assay or fourth-generation HIV antibody-antigen assays may be helpful in avoiding the administration of suboptimal treatment regimens to those who are acutely HIV infected. Further research is needed to optimize the delineation of those who have become HIV infected when using antiretroviral chemoprophylaxis.

WHO WILL PRESCRIBE PREP AFTER PEP?

Diverse practitioners may play an important role in the PEP to PrEP transition. PEP may initially be prescribed by acute responders, such as practitioners in emergency departments, but ongoing care for persons who transition to PrEP will likely be more feasible in ambulatory primary care settings. High rates of attrition between initial PEP care in emergency departments and follow-up visits in infectious disease clinics suggest that dedicated resources may be required to ensure effective transitions to chronic care settings [31]. For patients who successfully establish longitudinal care after initiating PEP, interventions to ensure that counseling about PrEP occurs, such as automated prompts in electronic health records or clinical decision aids to facilitate patient–provider discussions, could prevent missed opportunities for transitioning to PrEP and medication adherence [32].

No consensus exists as to which providers are optimally positioned to prescribe PrEP after PEP. HIV specialists may be early adopters of PrEP prescribing, as they routinely provide PEP to patients after referral from acute responders. Some specialists have counseled HIV-discordant couples who engage in condomless intercourse. However, recent studies have found that many HIV specialists express positive attitudes toward PrEP provision but few have prescribed PrEP, and many do not intend to do so [33, 34], in part because they believe that primary care providers (PCPs) or STI specialists are more likely to have contact with most high-risk, HIV-uninfected persons presenting to care. However, PCPs may require further training before prescribing antiretroviral medications, and STI clinics are generally not structured to provide longitudinal care, creating a “purview paradox” in which few providers adopt PrEP prescribing into practice [35].

OPTIMIZING THE PEP–PREP TRANSITION: AREAS FOR FURTHER RESEARCH

Prior to transitioning from PEP to PrEP, clinicians should evaluate candidates for medical conditions that could predispose them to adverse effects from using tenofovir-emtricitabine [23], with specific attention to renal and bone disease given the experience when treating HIV-infected patients. Longer-term studies to ascertain whether tenofovir-emtricitabine PrEP use predisposes to osteopenia are needed [23]. Serologic testing for hepatitis B infection is important in patients who have not been vaccinated, as long-term tenofovir-emtricitabine may protect users from HIV acquisition and can be treatment for chronic hepatitis B, when indicated. Patients with hepatitis B who initiate tenofovir-emtricitabine should be monitored for acute hepatitis flares if they discontinue treatment [36]. PrEP guidelines recommend STI screening every 3–6 months if patients engage in condomless sex, even if they are asymptomatic [23]. Incident syphilis or rectal STIs have been associated with HIV acquisition and should prompt intensive risk-reduction counseling [37, 38].

HIV testing every 2–3 months is recommended to mitigate the likelihood of prolonged tenofovir-emtricitabine use after HIV diagnosis, which could select for drug resistance mutations, although in PrEP efficacy studies, resistance mutations were rarely detected when participants became HIV infected [39, 40]. For persons who had difficulty adhering to their PEP

including serial risk assessment, HIV and STI testing, and counseling.

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course or who have episodic risks, more parsimonious event-driven PrEP studies are under way [41], but for the time being, daily use is recommended.

Risk-reduction counseling is recommended for patients using PEP and PrEP. The CDC has compiled a directory of evidence-based, behavioral risk-reduction interventions that may complement PEP and PrEP programs; many of these interventions offer freely accessible training materials for reproducing group or individual-level interventions in clinic settings (http://effectiveinterventions.org). Understanding the best ways to integrate existing or novel, culturally tailored behavioral interventions with chemoprophylaxis represents an important area for future HIV prevention research.

CONCLUSIONS

Antiretroviral chemoprophylaxis represents an important step forward in efforts to curb the HIV epidemic. A strong rationale exists for transitioning individuals who engage in repeated risks from utilizing PEP toward PrEP as part of comprehensive HIV prevention programs. However, numerous knowledge gaps exist, including how best to predict a person’s future risk after PEP, the optimal time to initiate PrEP after completing PEP, strategies to engage providers to provide PrEP after PEP, and best practices for monitoring and counseling patients. These questions can best be addressed by further research.

Notes

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