SUPPLEMENT ARTICLE

Optimizing Adherence to Preexposure and Postexposure Prophylaxis: The Need for an Integrated Biobehavioral Approach

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Preexposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) has been shown to be effective in preventing transmission of human immunodeficiency virus (HIV). A dose-response relationship between adherence and HIV transmission is illustrated in the current PrEP literature, and adherence interventions for PrEP may be useful, although currently few effective programs have been developed and tested. There is a paucity of randomized controlled trials testing PEP adherence interventions, and further research is needed. We conclude by proposing the importance of tailoring adherence counseling to address psychosocial factors and mental health stressors that may negatively affect adherence.

Keywords. PrEP; PEP; adherence; HIV; mental health.

Preexposure prophylaxis (PrEP) and postexposure prophylaxis (PEP) have been shown to protect against simian retroviral acquisition in animal models, and, more recently, have been shown to be effective in preventing human immunodeficiency virus (HIV) transmission in humans [1, 2]. Recent studies have demonstrated PrEP and PEP to be successful deterrents of infection [3–5], but adherence to antiretroviral regimens remains necessary for optimizing effectiveness. In this commentary, we evaluate what is known about adherence to PrEP and PEP, and discuss the role of psychosocial factors. Building on this discussion, we suggest future research directions for these biomedical HIV prevention interventions.

ADHERENCE TO AND EFFICACY OF PREP

A dose-response relationship between adherence and HIV transmission is illustrated across several PrEP efficacy trials [3, 4, 6]. In the Iniciativa Profilaxis Preexposición (iPrEX) trial [4], the only efficacy study of PrEP in men who have sex with men (MSM) and transgender women, the risk of HIV acquisition in the PrEP arm was decreased by 44% compared with those in the placebo arm. Roughly half of the cohort had drug detected at any time interval. Pharmacological modeling suggested that PrEP efficacy was 92% when any active drug was detected in blood, and drug levels consistent with daily use could potentially result in 99%–100% protection [4]. An open-label extension from iPrEX found that when blood concentrations indicated use of 4 or more tablets per week, no participants became infected [7]. This dose-response relationship for PrEP is also demonstrated in studies of heterosexuals in Africa and Thai injection drug users (IDUs). In the Partners PrEP trial in East Africa, PrEP efficacy was 67% for oral tenofovir disoproxil fumarate (TDF) alone and 75% for TDF coformulated with emtricitabine (TDF-FTC). However, efficacy increased to 86% with TDF, and 90% when TDF-FTC was detectable in blood [3]. Also, in an ancillary adherence study, when monitoring pill usage and using adherence counseling, efficacy of TDF-FTC rose to 100% [6]. In a randomized controlled trial (RCT) of TDF PrEP vs placebo among individuals who inject drugs in Bangkok [8], efficacy was 50%, but when drug was detectable, the estimated efficacy rose to

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74%. Furthermore, poor adherence has been cited as the primary contributing factor in PrEP studies that did not demonstrate efficacy, such as the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study [9, 10], which examined both oral and topical tenofovir-based PrEP in African women, and the FEM-PrEP study in African women, which only examined oral TDF-FTC vs placebo [10]. Both trials recruited at-risk women with high seroconversion rates and low adherence, and were stopped by their respective data and safety monitoring boards due to lack of efficacy. Each trial found low levels of drug in participants' blood. In sum, it appears that low levels of adherence may account for the lack of efficacy seen in 2 of the 6 PrEP efficacy trials.

Given that adherence appears to be crucial for PrEP efficacy, counseling interventions to enhance adherence may be useful in improving the efficacy of this prevention intervention [11]. Successful approaches such as the ancillary adherence study in the Partners PrEP trial provided additional counseling for individuals with <80% adherence, using a combination of approaches, including cognitive behavioral therapy, motivational interviewing, assistance with problem solving, and focused relationship counseling [7, 11]. In the Bangkok Thai IDU PrEP study, individualized risk-reduction and adherence counseling may have helped to achieve improvements in PrEP adherence [8]. Conversely, some have suggested that the negative results in the FEM-PrEP and VOICE trials may have been partially due to limitations in addressing culturally specific barriers to optimal PrEP adherence [12]. The lack of success in some of the recent PrEP studies suggests that new evidence-based interventions to enhance PrEP adherence among at-risk people, particularly populations in generalized epidemic settings, need to be further developed and tailored. To improve such interventions, it may be necessary for additional formative work to better understand and address real-life barriers that interfere with people's ability to achieve optimal adherence.

Psychosocial Barriers to PrEP Adherence

Psychosocial problems may negatively affect people's ability to adhere to PrEP. One psychosocial concern that has been identified as potentially impacting PrEP adherence is internalized HIV stigma [7, 13–15]. Qualitative data suggest that some individuals who could benefit from PrEP have concerns that their use of PrEP could be interpreted by others as an admission that they engage in HIV risk behavior, or that PrEP use could lead others to believe that they are HIV infected [7, 15, 16]. Adherence interventions that address these types of stigma may be helpful in enabling potential users being comfortable taking PrEP. Mental health problems may also contribute to poor adherence. Depression has been shown to be highly prevalent in some populations that are at increased risk for HIV infection, such as MSM [17] or substance users. Given that depression is consistently associated with antiretroviral therapy (ART) nonadherence in HIV-infected individuals [18] and can interfere with self-care, it is reasonable to posit that depressive symptoms may impact PrEP initiation and adherence [19]. Interventions that address depressive symptoms and other psychosocial issues, such as posttraumatic stress, may aid in increasing adherence [20].

Substance use may also create barriers to PrEP adherence; however, to date, there is little research on this association. Given the similar issues raised when using ART to treat HIV-infected people, and using ART for prevention, substance use is likely to affect adherence to PrEP in similar ways as it influences adherence to standard ART [19, 21]. Historically, individuals with active substance abuse have been less likely to be prescribed or to start ART [22], partly influenced by medical providers' reluctance to prescribe based on assumptions that these patients would be less adherent [23, 24]. Additionally, active substance use has been shown to be associated with worse adherence to ART than among those who do not use recreational drugs [18, 23, 25], and thus, it is reasonable to suspect that active substance users may experience similar obstacles with accessing PrEP, and with adherence, once provided with medication.

ADHERENCE TO AND EFFICACY OF PEP

Similarly to PrEP, low levels of adherence to PEP may reduce the effectiveness of the intervention, and also may jeopardize its cost-effectiveness [26]. There is a paucity of literature establishing ideal levels of adherence to PEP and consequently how to promote adherence for at-risk individuals. In a recent review, studies of PEP among individuals with nonforcible sexual exposure to HIV demonstrated an average of 78% adherence [27]. A recent meta-analysis assessing completion of PEP therapy in various clinical trials over the past 10 years showed rates ranging from 48% to 88% [28].

To the best of our knowledge, there are no guidelines for an effective minimal level of adherence to PEP, although 3 recent RCTs [29–31] attempted to measure adherence and set a standard of care while also testing adherence counseling interventions. The results of each RCT pointed in the direction of benefit, although none achieved statistical significance in their main effects. Also, importantly, in all 3 cases, relatively low levels of adherence were reported (38%–54%). Counseling-based programs for PEP have focused on risk avoidance and screening [32], and the aforementioned RCTs included adherence counseling. Roland et al [31] suggested that risk reduction and PEP adherence counseling may be most helpful for individuals with high levels of HIV risk behaviors. Abrahams et al [29] assessed telephone-based psychosocial support and utilized a leaflet and adherence diary to support victims of sexual assault in South Africa. Finally, Bentz et al [30] utilized counseling that focused on treatment of PEP-related

stress management and individual perception of treatment over the course of 4 sessions.

DISCUSSION

Although PEP and PrEP are approaches that rely on antiretrovirals for chemoprophylaxis, there are different considerations related to counseling. For most individuals who present for PEP, their exposure may be perceived as a one-time event, (eg, the condom broke, or a person was sexually assaulted). The clinician needs to attend to the acute anxiety that may accompany the exposure and then counsel the patient that high levels of adherence for a short interval will lead to protection. For PrEP, the presumption is that risk is recurrent, so the clinician needs to assess the readiness of a patient to be adherent to chemoprophylaxis for an extended period of time, and may need to periodically monitor to assess if continued medication is warranted. Although PEP and PrEP may often be seen as very different approaches for HIV prevention, some individuals who present for PEP may be engaging in behaviors that put them at continued risk for HIV acquisition, and clinicians should be prepared to determine whether a PEP user may subsequently benefit from PrEP.

Because of these complexities in treatment, simple adherence counseling (eg, explaining the benefits of adherence to medication) may not be enough to create substantial improvements in adherence [3, 15, 29, 31], particularly when medicine is used prophylactically. Individuals who are candidates for PEP or PrEP are generally healthy, and may not be as motivated to take medication as HIV-infected patients, who may perceive adherence being important in maintaining their health. Although there are currently limited data regarding psychosocial predictors of PrEP and PEP nonadherence, it seems reasonable that predictors will be similar to those detected when ART is used for treatment. For example, individuals at highest risk of nonadherence may need behavioral interventions that can concurrently address multiple facets of individuals' lives and not just their medication use (also see [33]).

One potential solution to this problem may be a stepped-care model, where assessment of individuals' level of risk for HIV infection and their burden of psychosocial problems can dictate the extent and range of counseling goals as well as the use of other modalities, ranging from cognitive-behavioral therapy to drug treatment programs. Such a model would encourage clinicians to work with behavioral interventionists to address PrEP users' problems, resulting in tailored adherence and risk reduction interventions for each individual. For example, individuals with fewer psychosocial problems may not require an extensive counseling intervention and may be assisted best with basic adherence counseling such as that including information, motivation, and behavioral skills building [34, 35]. However, for individuals who present with co-occurring psychosocial problems, these issues may interfere with the ability to benefit from adherence counseling, thereby necessitating more intensive, evidence-based interventions that target both adherence and reduction of the burden of their psychosocial problems [11, 19]. This approach is congruent with that advocated by Amico et al [12]: It is necessary to understand PrEP and PEP as interventions that require a tailored biobehavioral approach rather than as exclusively biomedical interventions in order to better understand the intricate web of factors influencing adherence to prophylactic medication and to optimize the likelihood that the combined modalities will result in increased protection against HIV infection.

Notes

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