Open Forum Infectious Diseases

TOP QUESTIONS IN ID

Top Questions in ID: Pre-exposure Prophylaxis for HIV

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HIV pre-exposure prophylaxis (PrEP) is highly efficacious at preventing HIV acquisition. This review discusses ways to identify candidates for PrEP, recommended PrEP regimens, baseline and follow-up evaluations, applications of PrEP for HIV-serodiscordant couples, resources to address financial barriers, investigational strategies for PrEP, and educational resources for clinicians and patients.

Keywords. HIV; prevention; pre-exposure prophylaxis.

WHO ARE THE BEST CANDIDATES FOR PrEP?

Pre-exposure prophylaxis (PrEP) is a highly efficacious strategy for the prevention of HIV acquisition [1–8]. Daily coformulated tenofovir disoproxil fumarate and emtricitabine (TDF/FTC; Truvada) was US Food and Drug Administration (FDA) approved for the prevention of HIV in adults in 2012, and the US Centers for Disease Control and Prevention (CDC) released guidelines for its use in 2014 [9]. PrEP is recommended for those at elevated risk for HIV infection, including men who have sex with men (MSM), heterosexually active men and women, and people who inject drugs (PWID). For MSM, indications for PrEP include having an HIV-infected sexual partner, a recent bacterial sexually transmitted infection (STI), multiple sex partners, or engaging in condomless anal sex and/or transactional sex. For heterosexual men and women, indications include having an HIV-infected sexual partner or engaging in transactional and/or condomless sex with partners who are at substantial risk of HIV infection [9]. For PWID, indications include having an HIV-infected injecting partner, sharing injection equipment, and recent drug treatment (but currently injecting) [9]. The CDC estimates that 1.2 million Americans have indications for using PrEP [10], though only about 100 000 persons have been prescribed PrEP [11].

Taking a sexual history and asking about sexual and drug using behaviors in an open-ended and nonjudgmental manner is a critical first step for identifying PrEP candidates in health care settings, but this history is often not obtained [12]. In addition, many people who may benefit from PrEP do not recognize themselves as at risk for HIV infection [13, 14].

There are courses available through the National Network of STD Prevention Training Centers to increase providers' knowledge to better address their patients' sexual health (http://nnptc.org/resourcetags/sexual-history/), and there are several online tools for assessing an individual's risk that can be used by clients or providers (eg, https://wwwn.cdc.gov/hivrisk/estimator.html#, http://www.mysexpro.org/en/home/).

While these guidelines and tools are helpful, individual-level risk is not the only determinant of HIV risk, and criteria for PrEP in the USPHS guidelines will miss some MSM and other patients who may benefit from using PrEP. It is important to consider local epidemiology and HIV prevalence in sexual and drug using networks. For instance, black MSM are disproportionately impacted by HIV and STIs, despite having equivalent or lower individual-level risks [15, 16]. Despite this, uptake of PrEP among MSM of color is lower than that for whites [17–19]. PrEP uptake is also low among women [20], in part due to limited awareness of PrEP among women [21] and their providers [22]. It is critical for providers to consider demographic factors and address health disparities. In addition, some patients may feel uncomfortable disclosing HIV risk behaviors, and it is therefore reasonable to prescribe PrEP to patients who request it, regardless of self-reported risk.

WHAT IS THE BASELINE EVALUATION?

After assessing the risk of HIV acquisition, the provider should assess the patient's knowledge and interest in PrEP and describe how PrEP works, including the small but statistically significant risks of renal and bone toxicity [1, 3] and the possibility of a transient "start-up" syndrome characterized by mild gastrointestinal symptoms that typically resolve after several weeks [3]. Confirming that the patient is HIV-uninfected is a critical element of the baseline evaluation (Table 1). The provider should determine when the patient's last potential exposure to HIV occurred and should assess for signs or symptoms of acute HIV infection.

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Table 1. Baseline Evaluation and Recommended Follow-up Care for HIV Pre-exposure Prophylaxis

Baseline Evaluation	Comments
Document negative HIV test ≤1 week before initiating PrEP	Also document negative HIV RNA test if signs or symptoms of acute HIV or high-risk exposure to HIV in prior 4 weeks
Confirm that patient is at substantial risk of HIV infection	Elicit a comprehensive sexual health and drug use history using nonjudgmental language
Confirm creatinine clearance ≥60 mL/min	
Document serologic status for hepatitis B and hepatitis C	If susceptible to hepatitis B, provide vaccination. If has chronic active hepatitis B, then consider using TDF/FTC for both PrEP and treatment of hepatitis B
Perform comprehensive testing for bacterial sexually transmitted infections, including syphilis, gonorrhea, and chlamydia	Test for gonorrhea and chlamydia at all mucosal sites with potential exposure (ie, pharyngeal, rectal, and urogenital).
Conduct pregnancy test for women	Limited data are available on PrEP use during pregnancy; studies suggest PrEP is safe for women who are pregnant [53] or breastfeeding [54]; guidelines recommend that clinicians help pregnant women to make informed decisions about PrEP use
Consider bone density scan for patients with, or at high risk for, osteoporosis	Guidelines also recommend consultation with bone health specialist as appropriate
Assess eligibility for immunizations against additional vaccine-preventable sexually transmitted infections (human papillomavirus, hepatitis A and B, and invasive meningococcal disease)	Vaccinate eligible individuals
Prescribing PrEP medication	
Prescribe tenofovir disoproxil fumarate 300 mg plus emtricitabine 200 mg as a fixed-dose combination tablet, 1 tablet by mouth daily	Prescribe no more than a 90-day supply
Provide condoms and counseling for risk reduction and PrEP medication adherence	
Assess financial barriers to using PrEP	See Table 2 for resources to address financial barriers
Clinical monitoring and follow-up care while using PrEP	
Every 3 months, perform HIV test	After documenting negative HIV test, provide medication refills for no more than 90 days
Every 3 months, assess and support adherence	
Every 3 months, provide condoms and risk reduction counseling	
Every 3 months, test for sexually transmitted infections	
Every 3 months, perform pregnancy test for women	
Every 6 months, confirm creatinine clearance ≥60 mL/min	For persons with risk factors for renal harms (eg, prior renal disease, proteinuria, hypertension, diabetes, use of nephrotoxic medications), assess creatinine clearance and urinalysis every 3 months
On discontinuing PrEP[a]	
Conduct HIV test to assess whether HIV infection has occurred	
If HIV-infected, order resistance testing and link to HIV care	
If HIV-uninfected, provide risk reduction counseling	Link to risk reduction support services as indicated
If HIV-uninfected and infected with chronic hepatitis B, initiate treatment with alternative medication for hepatitis B	If hepatitis B treatment is not indicated, then monitor for flare of hepatitis B (ie, symptoms of acute hepatitis, elevated serum transaminases)

Abbreviations: PrEP, pre-exposure prophylaxis; TDF/FTC, tenofovir disoproxil fumarate and emtricitabine.

[a]Because of safety concerns, intolerance, patient request, or HIV infection.

Clinicians should document a negative HIV antibody test result within the week before initiating PrEP, ideally with a combination HIV Ag/Ab test. Oral rapid tests should not be used to screen for HIV infection before PrEP use because of lower sensitivity than blood tests. Some PrEP providers also obtain a plasma HIV RNA test at PrEP initiation, particularly in patients who might have very recent exposures and/or symptoms suggestive of acute HIV infection [9, 17, 23]. If there is a high clinical suspicion for acute HIV, PrEP should be deferred until HIV RNA test results are known as initiating PrEP during acute HIV can lead to the development of antiretroviral resistance mutations [1, 3].

Clinicians should determine renal function and test for infection with hepatitis B virus (HBV) and hepatitis C virus (Table 1). Patients with a creatinine clearance <60 mL/min should not start PrEP. Hepatitis B is not a contraindication to PrEP use; however, because both TDF and FTC are active against HBV, it is important to be cognizant of the patient's hepatitis B status and to ensure that liver function is closely monitored if PrEP is stopped because reactivated HBV infection can result in hepatic damage [24]. Providers should assess for risk factors for renal disease and screen patients for syphilis, gonorrhea (GC), and chlamydia (CT), including at extragenital sites, as the majority of extragenital infections are asymptomatic [25]. Women initiating PrEP should have a pregnancy test, and all patients should be counseled about the importance of adherence and counseled on how to optimize it [9]. Lastly, patients should be offered immunizations for vaccine-preventable STIs if they are eligible (Table 1).

Table 2. Financial and Educational Resources for HIV Pre-exposure Prophylaxis

Financial Resources	Description
Patient Access Network: http://www.panfoundation.org/hiv-treatment-and-prevention	Financial assistance for individuals with private insurance or Medicare and income <500% of federal poverty limit
Patient Advocacy Foundation – Co-Pay Relief: https://www.copays.org/diseases/hiv-aids-and-prevention	Financial assistance for individuals with private insurance or Medicare and income <400% of federal poverty limit
Gilead patient assistance programs: https://start.truvada.com/hcp/prep-cost	Co-pay assistance for patients with private insurance; medication assistance for uninsured patients with income <500% of federal poverty limit
Project inform: https://www.projectinform.org/pdf/PrEP_Flow_Chart.pdf	Succinct guide to navigating insurance and financial barriers when accessing PrEP
Educational resources	
US Public Health Service Clinical Practice Guidelines for PrEP: https://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf	Clinical practice guidelines for clinicians
Centers for Disease Control and Prevention, PrEP resources: https://www.cdc.gov/hiv/risk/prep/	Fact sheets, infographics, and videos for clinicians and patients; some information available in Spanish
AIDS education and training centers: https://aidsetc.org/topic/pre-exposure-prophylaxis	Slide sets, webinars, toolkits, and pocket guides about diverse topics relating to PrEP for clinicians and patients
Please PrEP Me: https://www.pleaseprepme.org/; *PrEP Locator:* https://prep-locator.org/	National search engines for PrEP providers by zip code
Project Inform: https://www.projectinform.org/prep/	Downloadable brochures and clinic posters and flow charts
Sexuality Information and Education Council of the United States (SIECUS): http://www.siecus.org/index.cfm?fuseaction=page.viewPage&pageID=1555	PrEP education and toolkit for youth-serving primary care providers
The Fenway Institute: http://thefenwayinstitute.org/prepinfo/	Information and videos about PrEP for patients
What is PrEP?: http://www.whatisprep.org/	Video about PrEP basics for patients; available in Spanish
Global Advocacy for HIV Prevention (AVAC): http://www.avac.org/prevention-option/prep	News about HIV prevention; global directory of active research and implementation studies for PrEP

Abbreviation: PrEP, pre-exposure prophylaxis.

WHAT IS THE RECOMMENDED REGIMEN?

The only recommended, FDA-approved regimen for PrEP is daily TDF/FTC. With daily adherence, this regimen is >95% effective for the prevention of HIV infection in MSM [5, 8, 26, 27]. Efficacy may be slightly lower in women [1, 28, 29], given that oral TDF achieves lower concentrations of tenofovir in the female genital tract than in colorectal tissues [30], and in PWID [2]. MSM are also likely to gain high levels of protection with at least 4 doses per week of TDF/FTC [26], whereas pharmacologic models suggest that women need to take at least 6 doses per week to gain protective benefits [30]. While 1 study found that event-driven PrEP (ie, PrEP taken only before and after possible sexual exposures to HIV) may be effective for MSM [7], this regimen is not FDA approved in the United States (nor recommended by the CDC) given concern about a lack of data in individuals with infrequent exposure to HIV [31].

WHAT DO YOU DO IF YOUR PATIENT CAN'T TAKE TDF/FTC?

If a patient cannot use TDF/FTC because of contraindications to using TDF, such as renal insufficiency or osteoporosis [9], there are currently no evidence-based alternative regimens available. In this situation, clinicians should counsel patients that condom use and/or safer sex [32] for sexual exposures and use of sterile syringes for injection drug use exposures are effective options until additional PrEP modalities become available (see the "Investigational Strategies" section below), or until patients no longer have contraindications to using TDF (eg, if their renal and bone parameters improve). In the unusual case that a patient cannot use TDF/FTC because of a contraindication to using FTC, then TDF monotherapy could be used as an alternative PrEP regimen for heterosexual partners of HIV-infected people and for PWID as there are data showing that mono-prophylaxis was effective in these populations [1, 2, 4]. The CDC does not recommend TDF monotherapy for MSM as studies have not tested the efficacy of this regimen for MSM [9].

WHAT IS THE RECOMMENDED FOLLOW-UP?

Individuals using PrEP should be screened for HIV at least every 3 months, and sooner if there is suspicion of acute HIV infection (Table 1). To support adherence to quarterly HIV testing, it is recommended that providers prescribe no more than a 90-day supply of PrEP at each visit. As some patients will face challenges with adherence and persistence with PrEP [33], clinicians should also assess and counsel about adherence at follow-up visits [9]. PrEP should be discontinued if the patient tests positive, and the patient should be linked promptly to HIV care and started on a therapeutic HIV regimen. PrEP users should also be screened regularly for STIs and should have renal function checked at least every 6 months. Those with risk factors for renal disease, for example, age >40 years, lower baseline creatinine clearance, and/or predisposing conditions (eg, diabetes mellitus, hypertension), should have creatinine checked more frequently [34, 35]. Women should be counseled about contraception and tested for pregnancy if indicated.

HOW OFTEN DO YOU MONITOR PATIENTS FOR SEXUALLY TRANSMITTED INFECTIONS?

STIs are commonly diagnosed in PrEP users [5–8]. Although the CDC PrEP guidelines recommend STI screening at least every 6 months, data from 1 MSM cohort suggest that screening every 6 months as opposed to quarterly will cause a delay in treatment for more than one-third of GC, CT, and syphilis infections [36]. In addition, more than 75% of CT and GC infections are missed if extragenital sites are not screened [36]. A recent modeling study supports the importance of regular STI screening for PrEP users and shows that quarterly STI screening could eventually reduce STI incidence among MSM at the population level [37].

WILL PATIENTS INCREASE THEIR SEXUAL RISK BEHAVIORS WHILE USING PrEP?

In randomized studies of PrEP, participants did not report increased HIV risk behaviors and did not have increased rates of STIs while using PrEP, suggesting that they did not engage in risk compensation (ie, increase their risk behaviors while using PrEP) [1, 2, 6, 26]. However, in a survey of patients receiving PrEP during clinical care, 41% of patients reported decreased condom use while using PrEP [5], underscoring the need for clinicians to engage in comprehensive risk reduction counseling with patients using PrEP. Even if patients increase their risk behaviors while using PrEP, this intervention is likely to provide substantial protective benefits against HIV acquisition when taken with high adherence [5], so patient reports of ongoing or increased risk taking are not reasons for clinicians to discontinue PrEP. Rates of STIs have increased among MSM and other priority populations in recent years [38], but these increases began prior to the availability of PrEP, so they are likely multifactorial in nature.

WHAT DO YOU DO IF YOUR PrEP CANDIDATE IS IN A MONOGAMOUS, HIV-SERODISCORDANT RELATIONSHIP?

HIV-infected persons who use antiretroviral treatment (ART) and achieve stable virologic suppression are at extremely low risk of transmitting HIV to their sexual partners [39–41]. Therefore, if HIV-infected partners in monogamous, serodiscordant relationships have achieved virologic suppression, the additional protection of PrEP for HIV-uninfected partners is minimal. However, HIV-uninfected persons could derive substantial protective benefits from using PrEP if their HIV-infected partners have not initiated ART or have not yet achieved durable virologic suppression from ART and/or have suboptimal treatment adherence. Additionally, nonmonogamous HIV-uninfected partners in serodiscordant relationships could benefit from PrEP.

WHAT IS THE ROLE OF PrEP IN CONCEPTION FOR HIV-UNINFECTED WOMEN? FOR HIV-UNINFECTED MEN?

HIV-uninfected women who wish to conceive children with HIV-infected male partners can use PrEP as part of a multicomponent strategy to reduce their risk of HIV acquisition. Additional components may include virologic suppression for their male partners, limiting condomless sex to peak fertility, screening and treatment of STIs, and intrauterine insemination after sperm washing to remove HIV from a male partner's semen [42–44]. For HIV-uninfected males, intrauterine insemination of their sperm into a female partner without intercourse can be used to achieve conception without risk of HIV transmission [42, 43]. Being circumcised will also decrease their risk of HIV acquisition. Prioritization of approaches to safer conception will depend on economic, structural, and personal factors, such as insurance status, access to assisted reproduction technologies, which may not be accessible to many individuals with socioeconomic challenges, and personal preferences.

WHAT DO YOU DO IF PATIENTS FACE CHALLENGES WITH PAYING FOR PrEP?

Patients with health care insurance may face substantial out-of-pocket costs for PrEP because of varying insurance coverage determinations for PrEP-related care and medications and/or because of high co-pays or deductibles. Insurance barriers may result in discontinuations of PrEP use, which have been associated with HIV seroconversion [45, 46]. Several resources are available to help cover the cost of PrEP medications and follow-up care (eg, clinical visits, laboratory tests) (Table 2). Of note, even though PrEP is costly, with TDF/FTC priced at over $10 000 annually, numerous modeling studies suggest that PrEP is cost-effective when used in subgroups with high rates of new HIV infections (eg, MSM engaging in high-risk behaviors). However, PrEP may not be cost-effective at current drug prices when used in other subgroups (eg, PWID, MSM with low-risk behaviors) [47–50].

WHICH TYPES OF CLINICIANS SHOULD PRESCRIBE PrEP?

Ideally, any clinician who provides health care to individuals at risk for HIV infection would be trained and prepared to prescribe PrEP. Infectious diseases physicians who provide care to persons living with HIV infection have an opportunity to provide PrEP to the sexual partners of their HIV-infected patients when appropriate; these physicians may also receive patient referrals from generalist colleagues with less experience prescribing antiretroviral medications. However, there are insufficient numbers of infectious diseases physicians to meet the demand for PrEP nationally, so it is important to engage and support additional clinicians to prescribe PrEP, including primary care clinicians (as part of routine preventive health care), providers at sexual health or family planning clinics, and others.

WHAT INVESTIGATIONAL STRATEGIES ARE UNDER STUDY FOR PrEP?

TDF/FTC is "PrEP 1.0"; that is, new regimens are being evaluated [51], with the goal of offering at-risk persons a range of

options, analogous to hormonal contraception. Tenofovir alefenamide (TAF) has been shown to cause less renal and bone toxicity than TDF [52], and TAF/FTC PrEP is under study in a randomized controlled trial, comparing it with TDF/FTC. Cabotegravir, an integrase strand transfer inhibitor that may be able to be administered as infrequently as every 8 weeks, is also being evaluated as PrEP [39]. Studies of immunoprophylaxis using parenterally administered monoclonal antibodies are also underway [37]. Each approach may offer some unique advantages—for example, less frequent dosing, fewer specific toxicities—but none of them are currently available, so optimization of adherence to daily TDF/FTC is the best way to ensure chemoprophylactic efficacy at present.

WHAT ARE ADDITIONAL EDUCATIONAL RESOURCES FOR CLINICIANS WHO PROVIDE PrEP CARE? ADDITIONAL RESOURCES FOR PATIENTS?

Numerous educational resources about PrEP are available for clinicians and for patients, including comprehensive clinical practice guidelines from normative bodies (eg, US Public Health Services [9]) and informational materials in diverse modalities (eg, videos, webinars, downloadable brochures) from various advocacy organizations devoted to HIV care and prevention (Table 2).

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