Introduction

Background

Despite decades of efforts to implement risk-reduction programs, approximately 40,000 persons are newly infected with HIV each year in the United States, making it clear that additional strategies are needed to reduce the number of new HIV infections.[1,2,3,4] The risk for an individual acquiring HIV is heterogeneous and may fluctuate between periods of high behavioral risk and periods of low or no risk. Thus, HIV prevention strategies must offer options that are tailored to a patient’s individual needs.[5] An expanding number of HIV prevention methods are being implemented worldwide and preexposure prophylaxis (PrEP) is now accepted as an important prevention strategy.[5,6] Indeed, expanded use of PrEP is a major component in the national initiative—Ending the HIV Epidemic: A Plan for the United States.[7]

Principles of PrEP

The concept of using medication prophylaxis to reduce the risk of acquiring an infectious disease is well established, including the use antiretroviral therapy to prevent maternal-child transmission of HIV.[6,8,9] The fundamental principle with current PrEP strategies used in the United States is that an individual who does not have HIV takes daily antiretroviral medications to prevent HIV acquisition in the event of an exposure to HIV (Figure 1).[5] Future strategies may include use of long-acting injectable antiretroviral medications or use of an antiretroviral-impregnated vaginal or cervical ring that consistently delivers antiretroviral medications to the genital mucosal surface. In the United States, PrEP is primarily used to prevent sexual transmission of HIV. In the absence of PrEP, sexual transmission of HIV can occur as HIV crosses the mucosal surfaces to infect susceptible cells (Figure 2). After consistently taking daily PrEPs, the cells near the genital mucosal surface achieve good intracellular concentrations of the active components of the antiretroviral medications and thereby block replication of HIV following a sexual contact with a person infected with HIV (Figure 3).[10]

Guidelines for PrEP

Findings from multiple PrEP clinical trials using oral tenofovir DF-emtricitabine (or tenofovir DF alone), have demonstrated safety and a substantial reduction in the rate of HIV acquisition for men who have sex with men (MSM),[11,12,13] men and women in heterosexual HIV-discordant couples,[14] heterosexual men and women recruited as individuals,[15] transgender women,[11,13] and people who inject drugs (PWID).[16] On the basis of these study results the Food and Drug Administration (FDA) approved tenofovir DF-emtricitabine for PrEP in 2012. Subsequently, in May 2014, the U.S. Public Health Service published a clinical practice guideline (Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2014) along with a Clinical Providers’ Supplement—commonly referred to as U.S. Public Health PrEP Clinical Practice Guidelines; 2017 updates for both of these guidelines have been issued.[10,17]
Major PrEP Studies

There have been multiple large, randomized, controlled trials investigating the efficacy of PrEP in groups with different risk factors as summarized below.

Men and Transgender Women who have Sex with Men

- **iPrEx**: The Preexposure Initiative (iPrEx) study was a phase 3, randomized, double-blind, placebo-controlled trial conducted in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States involving 2,499 males seronegative for HIV infection, including 29 (1%) who identified as male-to-female transgender, and who were at high risk for HIV acquisition.[11] Participants were randomly assigned to receive a daily oral dose of either the fixed-dose combination of tenofovir DF-emtricitabine or a placebo. All study participants (drug and placebo groups) were seen every 4 weeks for an interview, HIV testing, counseling about risk-reduction and adherence to PrEP medication doses, pill count, and dispensing of pills and condoms. This study documented 44% fewer new HIV infections among those prescribed daily tenofovir DF-emtricitabine for PrEP when compared to those who received placebo.[11] A secondary analysis of the iPrEx study data concluded that to achieve maximal effect at the population level, PrEP should be targeted to men and transgender women who report unprotected anal receptive sex.[18]

- **IPERGAY**: The ANRS Intervention Préventive de l’Exposition aux Risques avec et pour les Gays (IPERGAY) study was a phase 3, randomized, double-blind, placebo-controlled trial in France and Canada evaluating the efficacy of oral tenofovir DF-emtricitabine taken before and after sexual activity for the prevention of HIV among 400 sexually active men and transgender women without HIV infection who have unprotected anal sex with men.[13] Participants were evaluated at weeks 4 and 8, and then every 8 weeks thereafter, and at each visit all patients received a comprehensive package of risk reduction interventions. Adherence was measured by pill count, structured interviews, and, in some patients, by plasma emtricitabine levels. After a median follow-up of 9.3 months, the relative risk reduction in HIV infection was 86% in the tenofovir DF-emtricitabine arm.[13]

- **PROUD**: The Preexposure Option for Reducing HIV in the UK (PROUD) study was a phase 4, randomized, open-label study at 13 clinics in England evaluating the efficacy of daily oral tenofovir DF-emtricitabine for the prevention of HIV among sexually active men without HIV infection who had unprotected anal sex with men in the previous 90 days.[12] The 544 study participants were randomized to receive daily tenofovir DF-emtricitabine either immediately upon enrollment or after a deferral period of 1 year. The investigators assessed sexual risk behaviors and adherence via daily diaries and monthly questionnaires; plasma tenofovir samples were collected from some participants as an objective measure of adherence. The relative risk reduction in HIV infection in the immediate arm (participants who took tenofovir DF-emtricitabine daily) was 86%.[12]

Heterosexual Men and Women

- **Partners PrEP**: The Partners PrEP trial was a phase 3, randomized, double-blind, placebo-controlled study that enrolled 4,758 HIV-discordant heterosexual couples in Uganda and Kenya to receive either daily oral tenofovir DF, tenofovir DF-emtricitabine, or placebo for the prevention of acquisition of HIV by the uninfected partner.[14] The partners with HIV infection had a median CD4 count of 495 cells/mm$^3$ and were not being prescribed antiretroviral therapy because they were not eligible per local treatment guidelines. The trial was stopped after an interim analysis in mid-2011 showed statistically significant lower HIV transmission rates
in both the tenofovir DF and tenofovir DF-emtricitabine groups compared with the placebo group; investigators reported a 75% reduction in HIV infection among the partners who were HIV-seronegative and taking daily oral tenofovir DF-emtricitabine, and a 67% reduction among those taking only daily oral tenofovir DF.[14] Adherence was high, as measured by pills dispensed, pill count, and random plasma drug-level testing.

- **TDF2:** The Botswana TDF2 Trial, a phase 3, randomized, double-blind, placebo-controlled study of the safety and efficacy of daily oral tenofovir DF-emtricitabine, enrolled 1,219 heterosexual men and women in Botswana who were not infected with HIV.[15] In this study, daily oral use of tenofovir DF-emtricitabine resulted in a 62% reduction in HIV acquisition when compared with placebo. Adherence by pill count was 84% in both medication groups.

### Women

- **CAPRISA 004:** The Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 was a phase 2, double-blind, randomized, controlled trial that assessed the efficacy and safety of a 1% vaginal gel formulation of tenofovir (dosed pre-and post-intercourse) for the prevention of HIV acquisition in 889 sexually active women without HIV infection in urban and rural South Africa.[19] The HIV serostatus, safety, sexual behavior, and gel and condom use were assessed at monthly follow-up visits for 30 months. The study demonstrated that tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence.

- **FEM-PrEP:** The FEM-PrEP trial was a phase 3, randomized, double-blind, placebo-controlled study of the HIV prevention efficacy and clinical safety of daily oral tenofovir DF-emtricitabine among heterosexual women in South Africa, Kenya, and Tanzania.[20] Participants were seen at monthly follow-up visits, and study drug was discontinued among women who became pregnant during the trial. The trial was stopped in 2011, when an interim analysis determined that the trial would be unlikely to detect a statistically significant difference in efficacy between the two study groups. Adherence was low in this trial, with detectable plasma drug levels in less than 50% of the women assigned to tenofovir DF-emtricitabine.

- **VOICE:** The Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial was a phase 2, randomized, double-blind study comparing oral tenofovir DF, oral tenofovir DF-emtricitabine, and topical vaginal tenofovir antiretroviral regimens against corresponding oral and topical placebos among 5,029 heterosexual women without HIV infection enrolled in eastern and southern Africa.[21] Face-to-face interviews, audio computer-assisted self-interviews, and pill-count medication adherence were high in all 3 groups (84% to 91%); in contrast, when random plasma drug levels were obtained, the percentage of samples with detectable drug was less than 40% in all study drug groups and the drug levels declined throughout the study. Both the group receiving oral tenofovir DF and the group receiving topical tenofovir were stopped after interim analysis determined futility. The group receiving oral tenofovir DF-emtricitabine continued to study completion. No reduction in HIV acquisition was observed in any of the study arms when compared with placebo.

- **MTN-020-ASPIRE:** A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), also known as MTN-020, was a phase 3, double-blind, placebo-controlled trial that randomized 2,629 sexually active, HIV-uninfected women to receive a monthly self-inserted vaginal ring containing either 25 mg of sustained-release dapivirine (an investigational non-nucleoside reverse transcriptase inhibitor) or placebo.[22] The study was conducted in Malawi, South Africa, Uganda, and Zimbabwe. Adherence was measured by dapivirine levels in plasma and by residual dapivirine levels in used rings. Use of the dapivirine ring reduced overall
HIV incidence by 27%, and higher adherence rates correlated with greater HIV protection. The HIV protection differed with age, a relationship that correlated with adherence; the efficacy of HIV protection was 61% among women older than 25 years of age (a subgroup with high rates of adherence) compared with 10% protection among women younger than age 25 (a subgroup with lower markers of adherence).[22]

- **Ring**: The Ring study was a phase 3, double-blind, placebo-controlled trial in which 1,959 sexually active women were randomized (2:1) to receive a monthly self-inserted vaginal ring containing either 25 mg sustained-release dapivirine (an investigational non-nucleoside reverse transcriptase inhibitor) or placebo.[23] The study enrolled women from seven communities in Uganda and South Africa. Adherence was measured by dapivirine levels in plasma and by residual dapivirine levels in used rings. Women in the dapivirine ring group had an HIV incidence rate of 4.1 seroconversions per 100 person-years compared with 6.1 seroconversions per 100 person-years in the placebo group, corresponding to a 31% reduction in HIV incidence with the use of the dapivirine ring.[23] The HIV protection differed with age; the efficacy of HIV protection was 37% among women older than 21 years of age (a subgroup with high rates of adherence) compared with 15% among women younger than age 21 (a subgroup with lower markers of adherence).[23]

People who Inject Drugs (PWID)

- **Bangkok Tenofovir**: The Bangkok Tenofovir Study (BTS) was a phase 2/3, CDC-sponsored, double-blind, placebo-controlled trial that randomized 2,713 persons without HIV infection who inject drugs to receive either daily oral tenofovir DF or placebo.[16] All participants also received access to addiction support services, methadone programs, bleach for cleaning needles, condoms, and primary care medical services. After a medium follow-up time of 4.6 years, the relative risk reduction in HIV infection was 49% among study participants in the tenofovir DF arm; the relative risk reduction was 70% in a subgroup analysis of individuals with detectable plasma tenofovir levels.[16]
Indications for PrEP

Based on the clinical trial data, the U.S. Public Health Service PrEP Clinical Practice Guidelines recommend the use of PrEP as one HIV prevention option in the following groups:[10,17]

- **Men who have Sex with Men**: Sexually active adult men who have sex with men with substantial risk for HIV acquisition (sexual partner with HIV infection, recent bacterial sexually transmitted infection, high number of sex partners, history of inconsistent or no condom use, or commercial sex work).

- **Heterosexual Women and Men**: Sexually active adult heterosexual men and women at substantial risk of HIV acquisition (sexual partner with HIV infection, recent bacterial sexually transmitted infection, high number of sex partners, history of inconsistent or no condom use, commercial sex work, or in a high-prevalence area or network). In addition, for HIV serodiscordant couples who wish to conceive and in whom the woman is not infected, the woman’s use of PrEP during periconception may reduce the risk of HIV acquisition.[10]

- **Persons who Inject Drugs**: Adults who inject drugs at substantial risk of HIV acquisition (injecting partner with HIV infection, sharing injection equipment, recently in a medication-based drug treatment program).
Laboratory Evaluation and Counseling Prior to Receiving PrEP

Baseline Laboratory Studies

The U.S. Public Health Service PrEP Clinical Practice Guidelines clinical practice guideline recommend performing a risk assessment and baseline laboratory evaluation prior to prescribing PrEP.\[10\] In order to qualify for PrEP, an individual should have substantial, ongoing risk for HIV infection and a baseline laboratory evaluation that includes all of the following:

- A negative HIV antibody performed within a week prior to starting PrEP (note that oral rapid tests are not recommended for HIV testing prior to starting PrEP due to lower sensitivity for recent infection when compared with current recommended initial HIV screening tests).
- Serologic screening for hepatitis B infection and vaccination if hepatitis B nonimmune.
- Serologic screening for hepatitis C infection.
- An evaluation of renal function to confirm that calculated creatinine clearance is 60 mL/min or greater using the Cockcroft-Gault formula. Persons with an estimated creatinine clearance less than 60 mL/min should not receive tenofovir DF-emtricitabine for PrEP.
- Pregnancy test for women who may become pregnant.
- Note: for men who have sex with men receiving PrEP, some experts recommend also obtaining baseline hepatitis A serologic studies and immunizing individuals who do not have evidence of immunity against hepatitis A virus.

Baseline Evaluation for HIV, HBV, and Pregnancy

It is crucial to confirm the patient does not have HIV infection prior to starting PrEP because the two-drug PrEP regimen provides inadequate treatment for established HIV infection. Testing for hepatitis B is important because HIV PrEP medications also treat hepatitis B infection—an individual with active hepatitis B infection could develop a hepatitis flare following discontinuation of the PrEP medications.[24] A patient with active hepatitis B can still receive PrEP, but, upon discontinuation of PrEP, they should have hepatitis B treatment extended with a different medication, such as entecavir. Prior to starting PrEP, a pregnancy test should be obtained. The safety of PrEP in pregnant women has not been confirmed so in the setting of pregnancy, the risks must be weighed against the benefits. In addition, PrEP should not be prescribed to a woman who is breastfeeding.

Behavioral Risk Reduction Counseling

Because high medication adherence is critical to PrEP efficacy, but is often not achieved, patients should be encouraged and enabled to use PrEP in combination with other effective HIV prevention methods.[10] When PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to proven effective risk-reduction and support services (Table 1).[10] In addition, it is important that persons who inject drugs understand that taking tenofovir DF-emtricitabine does not reduce the risk of hepatitis C acquisition.
Recommended PrEP Regimen and Dosing

Tenofovir DF 300 mg coformulated with emtricitabine 200 mg (tenofovir DF-emtricitabine) taken as one tablet once daily is the recommended regimen in the United States for all groups taking HIV PrEP.\textsuperscript{[10,17]} Daily tenofovir DF-emtricitabine is the only medication regimen approved by the Food and Drug Administration (FDA) for PrEP and it is the only medication recommended for PrEP in the U.S. Public Health Service PrEP Clinical Practice Guidelines.\textsuperscript{[10]} Persons with an estimated creatinine clearance less than 60 mL/min should not receive tenofovir DF-emtricitabine for PrEP.\textsuperscript{[10]} Although a different strategy of using PrEP on demand before and after sexual activity was shown to be highly efficacious in the large IPERGAY trial,\textsuperscript{[13]} there are no U.S. guidelines that recommend using this approach. Although tenofovir DF alone was found to be effective in the Bangkok PrEP injection drug trial and in one trial of heterosexually active adults,\textsuperscript{[14,16]} it is not FDA-approved as a single medication for PrEP. The U.S. Public Health Service PrEP Clinical Practice Guidelines specifically recommends against using tenofovir DF alone for PrEP, even among persons who inject drugs.\textsuperscript{[10]} The fixed-dose medication tenofovir alafenamide-emtricitabine, which is similar to tenofovir DF-emtricitabine, is FDA-approved in combination with other antiretroviral medications for the treatment of persons with established HIV infection, but tenofovir alafenamide-emtricitabine is not FDA-approved for PrEP.
Time to Achieve Protection from PrEP

After initiating PrEP with tenofovir DF-emtricitabine, the medications must reach the body tissues and the medications must then undergo phosphorylation to function as an inhibitor of HIV replication. Available data in humans suggest that with oral ingestion of tenofovir DF maximal concentrations of the active drug tenofovir diphosphate are obtained in rectal tissues by about 7 days, cervicovaginal tissues at about 20 days, and blood by about 20 days.\[25,26,27] Nevertheless, these drug level data do not necessarily translate into clinical protection efficacy and the true time from initiation to protection remains unknown. Given the uncertainty of the timing of when PrEP becomes effective after starting daily tenofovir DF-emtricitabine, the U.S. Public Health Service PrEP Clinical Practice Guidelines do not provide a specific recommendation for the time to achieve protection from PrEP.\[10\]
Monitoring on PrEP

An individual taking tenofovir DF-emtricitabine daily for PrEP should have a number of laboratory studies obtained as part of routine follow-up evaluations. These follow-up evaluations should take place every 3 months to evaluate and support PrEP medication adherence, as well as to perform recommended screening laboratory studies. The U.S. Public Health Service PrEP Clinical Practice Guidelines recommend the following regarding laboratory monitoring in patients taking PrEP (Figure 4):[10]

- Repeat HIV testing and evaluation for signs and symptoms of acute HIV infection should be performed at least every 3 months (Table 2).[10,28] If, at any point, a patient develops a positive HIV antibody test, further evaluation should occur to determine if the patient taking PrEP has confirmed HIV infection.

- Pregnancy testing for women who might become pregnant while taking PrEP should be performed at least every 3 months. If a woman becomes pregnant (or is breastfeeding) while taking PrEP, the clinician prescribing PrEP should have a discussion with the patient and her prenatal medical provider about the risks and benefits of continuing PrEP during pregnancy. In the large PrEP trials, women discontinued PrEP if they became pregnant, thereby eliminating the possibility of evaluating the safety of taking PrEP during pregnancy. In contrast, significant experience now exists with the use of tenofovir DF-emtricitabine as a component of antiretroviral therapy for women with HIV infection who are pregnant and the data suggest no safety concerns.[29]

- Additional laboratory monitoring, at least every 6 months, should include testing for renal function with estimation of creatinine clearance as well as testing for sexually transmitted infections. Many experts would recommend increasing the frequency of testing for sexually transmitted infections to every 3 months. Screening should include all appropriate body sites for gonorrhea and chlamydia based on reported sexual risk.

- The monitoring guideline does not include a recommendation to repeat hepatitis B or hepatitis C testing while a patient is taking PrEP. Some experts recommend annual testing for hepatitis C based on sexual and drug use practices, as well as local epidemiology. Individuals tested at baseline who were non-immune to hepatitis B should receive vaccination against hepatitis B.
Acquisition of HIV While on PrEP

If HIV infection is documented to occur while an individual is taking PrEP, then a number of subsequent steps should occur.[10]

- Additional laboratory studies should be ordered that include an HIV RNA level (if not already performed as part of the diagnostic evaluation), a CD4 cell count, and an HIV genotype resistance assay (if the HIV RNA level is high enough to perform the genotype).
- Any person on PrEP with newly diagnosed HIV infection should receive a referral to a medical provider with significant HIV clinical experience, if the clinician prescribing PrEP is not an experienced HIV clinician. In addition, partner notification should occur with all persons newly diagnosed with HIV infection.
- Once a diagnosis of HIV is made, it is important the patient not remain on the two-drug tenofovir DF-emtricitabine PrEP regimen, which is not a fully suppressive antiretroviral regimen. The USPHS PrEP Clinical Practice Guidelines do not give specific recommendations regarding antiretroviral management of a patient who acquires HIV while taking PrEP. Experts have outlined two main options for transitioning to a fully suppressive antiretroviral regimen in a patient that has an adequate HIV RNA level to perform the genotype: (1) discontinue PrEP and defer starting three- or four-drug antiretroviral therapy following results of the HIV genotype return, or (2) immediately switch to a fully suppressive antiretroviral regimen and modify the regimen, if needed, when the results from the genotype become available. Most experts would prefer the latter of these two options.
Adherence and the Impact on Efficacy of PrEP

In the PrEP trials completed to date, adherence to PrEP has been the single most important factor that impacts efficacy [5, 30, 31] In the iPrEx trial, investigators measured intracellular levels of tenofovir diphosphate and emtricitabine triphosphate and found substantially higher intracellular drug levels in participants who did not acquire HIV than in those subjects who became infected with HIV during the study (Figure 5). [11] In the Partners PrEP trial, a relative reduction of 75% was seen in HIV acquisition for persons who were not infected with HIV and received tenofovir DF-emtricitabine; among patients randomized to tenofovir DF-emtricitabine, those who had a detectable blood level of tenofovir (a marker of adherence) had a 90% reduction in HIV acquisition compared with those with an undetectable tenofovir level. [14] With the other major PrEP studies that reported positive results with PrEP, the reduction in HIV acquisition was substantially higher with adherence-adjusted efficacy based on detection of tenofovir in blood (Figure 6). [32] In addition, in the FEM-PrEP and VOICE trials, investigators concluded that the lack of efficacy with tenofovir DF-emtricitabine PrEP likely resulted from very poor adherence among women participating in the trials. [20, 30] Ultimately, most PrEP trials found that high levels of adherence correlate with PrEP efficacy and regular adherence counseling is recommended for patients taking PrEP (Table 3). [10]
PrEP and Development of HIV Drug Resistance

Incidence of HIV Resistance in Persons Taking PrEP

Although development of drug resistance is a concern in an individual who acquires HIV infection while taking PrEP, in the large PrEP trials investigators have reported a low incidence of HIV resistance.[14, 33, 34] In the iPrEx study, none of the 48 persons taking tenofovir DF-emtricitabine who became infected showed resistance mutations based on standard clinical assays; 2 minor variant mutations were detected with deep sequencing.[34] In the Partners PrEP study, 5 of 63 seroconverters (7.9%) in the active PrEP arms of the study developed resistance, and resistance was more common in persons assigned to the tenofovir DF-emtricitabine arm compared with the tenofovir DF only arm.[33] In contrast to earlier results from Partners PrEP, which indicated that most cases of resistance involved subjects who initiated PrEP at a time when they had undiagnosed early HIV infection, this more recent analysis confirms that PrEP-associated resistance mutations can occur in association with PrEP breakthrough infections.[14, 33] In addition, transmission of multi-drug resistant HIV has occurred.[35] Nonetheless, based on the available data, overall PrEP-related HIV drug resistance is thought to be low as long as HIV infection is recognized promptly and PrEP medications are discontinued or changed to a fully suppressive antiretroviral regimen immediately upon discovery of HIV infection. An HIV RNA level and an HIV genotype resistance assay should be ordered promptly for any patient on PrEP who becomes HIV infected. In some instances, however, patients on PrEP may have HIV RNA levels below the range for reliable performance of HIV genotyping since they are receiving partial antiretroviral therapy with tenofovir DF-emtricitabine.

Impact of Resistance

A mathematical modeling study estimated that widespread use of PrEP in sub-Saharan Africa would lead to a minimal increase in resistance over time (overall increase of 7% in individuals with HIV infection over 20 years) and the significant benefit of a decrease in HIV prevalence as a result of widespread use of PrEP would trump the negative impact of a low-level increase in HIV resistance.[36] Furthermore, the study predicted that most drug resistance would result from antiretroviral therapy used for HIV treatment, not for PrEP.

Monitoring for HIV Infection to Prevent Resistance

To minimize the risk of developing resistance among persons taking PrEP, the U.S. Public Health Service PrEP Clinical Practice Guidelines recommend prescribing recommends prescribing no more than 90 days of medication at a time and repeating HIV antibody testing every 3 months, or sooner if the individual receiving PrEP develops symptoms of acute HIV.[10]
Adverse Effects of Tenofovir DF-Emtricitabine

In several large studies in which tenofovir DF-emtricitabine was used for PrEP, the medication was well tolerated and safe. The most common side effects reported in the PrEP studies were nausea and decreased appetite, primarily occurring in the first month of taking the drug.\[6,10\] These side effects led to mild weight loss in some subjects, which generally stabilized after the first month. Tenofovir DF can cause renal dysfunction, specifically a proximal tubulopathy, but renal adverse events in large trials of PrEP were either similar to or only slightly more common than with placebo, and resolved with discontinuation of the medication.\[37,38,39\] Nevertheless, extensive treatment experience with tenofovir DF when used as treatment for persons with HIV infection has shown the potential for tenofovir to cause nephrotoxicity. Accordingly, the U.S. Public Health Service PrEP Clinical Practice Guidelines recommend careful monitoring of renal function in all patients taking tenofovir DF-emtricitabine for PrEP.\[10\] Concern also exists regarding the effects of tenofovir DF on bone mineral density. Toxicity data from HIV PrEP studies have demonstrated a small and clinically insignificant decrease in bone mineral density in participants who took tenofovir DF-emtricitabine.\[40,41,42,43\] Findings from a recent study suggested the minor losses in bone mineral density that occurred in persons receiving PrEP were recovered within 12-18 months after stopping PrEP.\[44\] Although tenofovir DF could potentially impact bone density, routine baseline (or follow-up) bone density scanning is not recommended.
Use of PrEP and Changes in HIV-Related Risk Behavior

Critics of PrEP have argued that its use will lead to behavioral disinhibition and an increase in high-risk sexual and drug use practices, an effect labeled risk compensation.[11,45] Clearly many persons who use PrEP have been engaging in sexual practices that place them at risk for HIV prior to starting PrEP.[46] Indeed, multiple studies have reported the highest uptake and adherence to PrEP occurs among persons who engage in high-risk sexual behavior.[47] Moreover, data from several of the PrEP studies suggest that PrEP may actually reduce high-risk behavior, potentially resulting from the counseling accompanying the delivery of PrEP.[5] For example, in the iPrEx study of men who have sex with men and transgender women, there was a trend toward safer sex as measured by decreased number of receptive anal intercourse partners and lower rates of both syphilis and acute HIV infections (Figure 7).[45] In the Partners PrEP trial of heterosexual couples in Kenya and Uganda, the percentage of patients reporting sex without a condom decreased during the course of receiving PrEP.[14] In the TDF2 trial of heterosexuals in Botswana, the number of sex partners decreased during the course of the study while the percentage of patients reporting sex without a condom remained stable.[15] In the PrEP trial of persons who inject drugs in Thailand, rates of injecting drugs and sharing needles decreased at follow-up.[16] In contrast, in the Victorian PrEP Demonstration Project, participants had a significant reduction in condom use in conjunction with an increase in sexually transmitted infections during the first 12 months of follow-up.[48] It remains to be seen whether risk behavior may change in the non-trial setting where counseling may not be as extensive as occurred in the clinical trials setting. Most experts believe the HIV prevention value of PrEP outweighs any potential change in sexual practices that may occur while persons are receiving PrEP.
Discontinuing PrEP

There are a number of factors that may lead a patient to discontinue PrEP, including a decline in HIV risk activity, medication-related side effects, pill fatigue, a positive HIV test, or pregnancy. In general, PrEP is best used during periods of high behavioral risk for acquiring HIV, which may occur during a phase lasting months or even years, but it should not be viewed as a life-long prevention strategy.[6] Several key factors should be taken into consideration at the time of discontinuing PrEP:

- Upon discontinuation of PrEP, the U.S. Public Health Service PrEP Clinical Practice Guidelines recommend that repeat HIV testing should always be performed and the reason for discontinuing PrEP should be documented in the health record.[10] If, at a later point, an individual wants to restart PrEP, they should undergo the same evaluation as a person newly prescribed PrEP.
- For an individual planning to discontinue PrEP, some experts would recommend ideally continuing PrEP for a period of time after the last high-risk exposure prior to stopping (many experts recommend 28 days).
- If the individual discontinues PrEP for any reason other than becoming infected with HIV, they should continue to have HIV testing performed, linkage to HIV prevention support services, and risk reduction counseling.
- If a patient has a positive screening antibody test for HIV, further evaluation should include an HIV RNA level and HIV resistance testing (if the HIV RNA level is high enough). The individual with newly diagnosed HIV infection should be linked to appropriate HIV care (if the medical provider prescribing PrEP does not have HIV expertise) and undergo prompt evaluation for a full 3-drug antiretroviral treatment regimen.
- If an individual with chronic hepatitis B infection is taking tenofovir DF-emtricitabine for PrEP, discontinuing the medication could lead to a hepatitis B flare since HBV DNA levels can dramatically rebound.[24] Accordingly, in a patient with chronic hepatitis B infection who no longer will need PrEP, continued hepatitis B treatment may be necessary to control hepatitis B infection.
Transitioning from Nonoccupational PEP to PrEP

General Approach to Transition from nPEP to PrEP

From a practical standpoint, many individuals who present for nonoccupational postexposure prophylaxis (nPEP) following a sexual or injection-related exposure to HIV may be candidates for PrEP, particularly if they have ongoing behaviors that place them at risk for HIV acquisition.[10, 49, 50] The U.S. Public Health Service PrEP Clinical Practice Guidelines specifically address the use of PrEP in person seeking nonoccupational PEP.[10] Persons who repeatedly seek nPEP should be evaluated for possible PrEP. The guideline do not address the practical implementation of this transition from nonoccupational PEP to PrEP. Thus, if a patient receiving nonoccupational PEP was interested in receiving PrEP, ideally the patient would need to wait to confirm current negative HIV status following the high-risk exposure for which they received nonoccupational PEP. With use of a fourth-generation combined HIV p24 antigen-HIV antibody test, this would usually consist of testing out to 3 months after the exposure.[51] In addition, to transition to PrEP, no additional high-risk exposures to HIV should have occurred in this 3-month time period. Some experts would argue that HIV could be effectively ruled out in 4 to 6 weeks after the exposure with use of new fourth-generation HIV antigen-antibody tests, but others have pointed out that if the patient acquired HIV infection, the 28-day nonoccupational PEP regimen could delay the time to positivity for a fourth-generation HIV antigen-antibody test.

Immediate Transition from nPEP to PrEP

Alternatively, the U.S. Public Health Service PrEP Clinical Practice Guidelines propose that if HIV exposures are not isolated, and the person seeking nPEP is highly motivated to prevent HIV acquisition, clinicians could consider beginning PrEP immediately upon completing the 28-day nonoccupational PEP regimen.[10] For some patients, not inserting a gap between nonoccupational PEP and PrEP may be reasonable if they have ongoing high-risk HIV activity and could be at significant risk of acquiring HIV during a gap period prior to starting PrEP. The concern with direct transmission without a gap is that a patient could acquire HIV from the exposure warranting nonoccupational PEP (a three-drug regimen) and transition to PrEP (a two-drug regimen) would result in partial treatment of HIV infection, with likely generation of drug resistance. Some experts advocate for HIV RNA testing prior to prescribing PrEP in patients at high risk for acute HIV infection.[49] In general, these situations should be evaluated on a case-by-case basis and whenever possible, with input from expert consultation.
**Future Studies**

Further studies are underway to investigate different delivery systems for PrEP as well as different active antiretroviral agents. Some of these novel PrEP candidates include maraviroc vaginal gel, tenofovir anal gel, topical raltegravir, tenofovir vaginal ring, dapivirine plus maraviroc vaginal ring, tenofovir DF-emtricitabine vaginal tablet, oral rilpivirine, oral maraviroc, and long-acting oral and injectable antiretrovirals, including the integrase inhibitor cabotegravir.[52, 53, 54, 55, 56] Similar to other areas of preventative health (e.g. contraception for women who want to avoid pregnancy), HIV prevention strategies should employ multiple options that are tailored to a patient’s needs.[5] Information regarding PrEP studies can be found on the [PrEP Watch](#) resource from the AIDS Vaccine Advisory Council (AVAC).
Summary Points

- PrEP is a safe and effective prevention option for those individuals whose sexual or drug use behaviors place them at substantial risk of acquiring HIV infection, including sexually active adult men who have sex with men, sexually active heterosexuals in HIV-serodiscordant partnerships, transgender women, and persons who inject drugs.
- The recommended PrEP regimen is tenofovir DF-emtricitabine taken once daily on a regular basis; tenofovir DF-emtricitabine is the only medication regimen recommended and approved by the FDA for PrEP.
- A risk assessment and baseline laboratory evaluation is required prior to prescribing PrEP.
- Clinicians are advised to prescribe no more than 90 days of PrEP medication at a time, and refills should be given only after repeat HIV testing is negative and medication adherence has been assessed.
- Renal monitoring is required at least every 6 months for patients taking PrEP due to the risk of tenofovir DF-induced nephrotoxicity.
- For HIV discordant couples in which the female is uninfected and who wish to conceive, the use of PrEP by the female partner during periconception may help reduce the risk of HIV acquisition; both FDA labeling and perinatal guidelines currently support this indication.
- Mothers taking PrEP should be advised not to breastfeed.
- Adherence to the PrEP medication has been the single most important factor that impacts efficacy in the clinical trials of PrEP.
- Overall PrEP-related resistance is thought to be low as long as HIV infection is recognized promptly and PrEP medications are discontinued immediately upon discovery of infection.
- If an individual with chronic hepatitis B infection is taking PrEP, discontinuing tenofovir DF-emtricitabine could lead to a serious hepatitis B flare.
- When discontinuing PrEP, repeat HIV testing should always be performed and the reason for discontinuation should be documented in the health record.
Citations


References


The principle of preexposure prophylaxis, as recommended in the United States, is to take antiretroviral medications on a regular and consistent schedule (daily) to provide protection against any subsequent exposure to HIV.

Illustration by David H. Spach, MD
When preexposure prophylaxis is taken, the antiretroviral medications can provide protection when exposures to HIV occur.

Illustration by David H. Spach, MD
**Figure 2 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface (Image Series) - Figure 2 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface**

**Image 2A: Normal Genital Mucosal Surface**

Illustration by David H. Spach, MD
Submucosal cells that play a role in early HIV infection include CD4 T-lymphocytes, dendritic cells, and macrophages.

Illustration by David H. Spach, MD
Although many strains of HIV may come into contact with the genital mucosal surface, usually only one (or a few) cause infection. This transmission virus is often referred to as the founder virus. Most initial transmission involves R5-tropic HIV strains that infect CCR5-positive CD4 cells.

Illustration by David H. Spach, MD
Once cellular infection with HIV takes place, rapid HIV replication and spread to adjacent cells can occur.

Illustration by David H. Spach, MD
After 1-2 days of taking oral tenofovir DF-emtricitabine, the intracellular levels of tenofovir diphosphate and emtricitabine triphosphate will begin to rise. These medications must undergo phosphorylation to exert their inhibition of HIV.

Illustration by David H. Spach, MD
Figure 3 (Image Series) - Preexposure Prophylaxis and Prevention of Sexual Transmission of HIV
Image 3B: Intracellular Concentrations of Tenofovir and Emtricitabine after 21 Days

After consistently taking oral tenofovir DF-emtricitabine as PrEP for 21 days, the submucosal cells susceptible to HIV infection should have high intracellular levels of tenofovir diphosphate and emtricitabine triphosphate, the active forms of these drugs.

Illustration by David H. Spach, MD
In an individual taking PrEP who has high intracellular levels of tenofovir diphosphate and emtricitabine triphosphate, HIV infection of submucosal cells results in a dead end, since the medications block HIV reverse transcription. Thus, in this situation, HIV transmission is blocked since HIV cannot replicate and spread to other cells.
Figure 4 Recommended Laboratory Monitoring for Persons Receiving Preexposure Prophylaxis


<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Baseline</th>
<th>Every 3 months</th>
<th>At least every 6 months</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV screening assay</td>
<td>✓</td>
<td></td>
<td></td>
<td>Consider need for HIV RNA PCR</td>
</tr>
<tr>
<td>HBV antibody panel and HCV antibody</td>
<td>✓</td>
<td></td>
<td></td>
<td>Offer HBV vaccination if not immune</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>Avoid PrEP if eCrCl &lt;60 mL/min</td>
</tr>
<tr>
<td>STI testing</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>Include oral/rectal screen for MSM if risk</td>
</tr>
<tr>
<td>Pregnancy test for women*</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: eCrCl = estimated creatinine clearance; STI = sexually transmitted infections
*The safety of PrEP in pregnancy has not been established
Figure 5 Intracellular Drug Levels in Persons Receiving Tenofovir DF-Emtricitabine

Abbreviations: FTC-TP = emtricitabine triphosphate; TFV-DP = tenofovir diphosphate. In the iPrEx Study, investigators measured intracellular levels of emtricitabine triphosphate and tenofovir diphosphate, the active forms of these drugs, in study participants randomized to the tenofovir DF-Emtricitabine group.


A. Intracellular Emtricitabine-Diphosphate Level

<table>
<thead>
<tr>
<th>FTC-TP (pmol/10⁶ cells)</th>
<th>Case (HIV-positive)</th>
<th>Control (HIV-negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/34 Detectable</td>
<td>9%</td>
<td>22/42 Detectable</td>
</tr>
</tbody>
</table>

B. Intracellular Tenofovir-Diphosphate Levels

<table>
<thead>
<tr>
<th>TFV-DP (fmol/10⁶ cells)</th>
<th>Case (HIV-positive)</th>
<th>Control (HIV-negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2/34 Detectable</td>
<td>6%</td>
<td>21/42 Detectable</td>
</tr>
</tbody>
</table>

Adjusted relative risk reduction (any detectable level) = 95%
Figure 6 Estimates of PrEP Efficacy Adjusted for Adherence

In several of the key PrEP studies, efficacy is adjusted upward significantly when analyzing the data for persons with assumed adherence based on detectable antiretroviral drug levels.

Figure 7 Sexual Behavior During iPrEx Study

This graphic shows the mean number of receptive anal intercourse (RAI) partners in the past 3 months by perceived treatment group (tenofovir DF-emtricitabine or placebo). Overall during the study, there was a trend in fewer number of RAI partners and the decline appeared to be greater in those participants who perceived they were taking placebo.


Mean # of Receptive Anal Intercourse Partners in Past 3 Months in iPREX

RAI= receptive anal intercourse; TDF-FTC= tenofovir-emtricitabine
Table 1. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2014

Key Components of Behavioral Risk-Reduction Counseling

<table>
<thead>
<tr>
<th>Establish trust and 2-way communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide feedback on HIV risk factors identified during sexual and substance use history taking</td>
</tr>
<tr>
<td>• Elicit barriers to, and facilitators of, consistent condom use</td>
</tr>
<tr>
<td>• Elicit barriers to, and facilitators of, reducing substance abuse</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Support risk-reduction efforts</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assist patient to identify 1 or 2 feasible, acceptable, incremental steps toward risk reduction</td>
</tr>
<tr>
<td>• Identify and address anticipated barriers to accomplishing planned actions to reduce risk</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitor behavioral adherence in a non-judgmental manner</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acknowledge the effort required for behavior change</td>
</tr>
<tr>
<td>• Reinforce success</td>
</tr>
<tr>
<td>• If not fully successful, assess factors interfering with completion of planned actions and assist patient to identify next steps</td>
</tr>
</tbody>
</table>

Source:
<table>
<thead>
<tr>
<th>Population Group</th>
<th>Overall (n = 375)</th>
<th>Male (n = 355)</th>
<th>Female (n = 23)</th>
<th>Sexual (n = 34)</th>
<th>Injection Drug Use (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>75</td>
<td>74</td>
<td>83</td>
<td>77</td>
<td>50</td>
</tr>
<tr>
<td>Fatigue</td>
<td>68</td>
<td>67</td>
<td>78</td>
<td>71</td>
<td>50</td>
</tr>
<tr>
<td>Myalgia</td>
<td>49</td>
<td>50</td>
<td>26</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>Skin rash</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td>51</td>
<td>21</td>
</tr>
<tr>
<td>Headache</td>
<td>45</td>
<td>45</td>
<td>44</td>
<td>47</td>
<td>30</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>40</td>
<td>40</td>
<td>48</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>Cervical adenopathy</td>
<td>39</td>
<td>39</td>
<td>39</td>
<td>41</td>
<td>27</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>30</td>
<td>30</td>
<td>26</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>Night sweats</td>
<td>28</td>
<td>28</td>
<td>22</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27</td>
<td>27</td>
<td>21</td>
<td>28</td>
<td>23</td>
</tr>
</tbody>
</table>

Source:


**Key Components of Medication Adherence Counseling**

<table>
<thead>
<tr>
<th>Establish trust and bidirectional communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Medication dosage and schedule</td>
</tr>
<tr>
<td>• Management of common side effect</td>
</tr>
<tr>
<td>• Relationship of adherence to the efficacy of PrEP</td>
</tr>
<tr>
<td>• Signs and symptoms of acute HIV infection and recommended actions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Support adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tailor daily dose to patient’s daily routine</td>
</tr>
<tr>
<td>• Identify reminders and devices to minimize forgetting doses</td>
</tr>
<tr>
<td>• Identify and address barriers to adherence</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitor behavioral adherence in a non-judgmental manner</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normalize occasional missed doses, while ensuring patient understands importance of daily dosing for optimal protection</td>
</tr>
<tr>
<td>• Reinforce success</td>
</tr>
<tr>
<td>• Identify factors interfering with adherence and plan with patient to address them</td>
</tr>
<tr>
<td>• Assess side effects and plan how to manage them</td>
</tr>
</tbody>
</table>

Source:
