Preexposure Prophylaxis (PrEP)

Introduction

Background

Despite decades of efforts to implement HIV-related risk-reduction programs in the United States, the number of new HIV infections has not declined in recent years, leveling off at approximately 38,000 new infections per year (Figure 1).[1,2,3,4] Furthermore, significant geographic and demographic disparities exist within the United States HIV epidemic, with the bulk of new infections occurring among young black and Hispanic men who have sex with men, particularly in the South.[5] It is clear that additional efforts are needed to reduce the number of new HIV infections. 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.[6] An expanding number of HIV prevention methods are being implemented worldwide and preexposure prophylaxis (PrEP) is now accepted as an important prevention strategy.[6,7] The expanded use of PrEP is a major component in the national initiative—Ending the HIV Epidemic: A Plan for the United States.[8]

Principles of PrEP

The concept of using medication prophylaxis to reduce the risk of acquiring an infectious disease is well established, including the use of antiretroviral therapy to prevent maternal-child transmission of HIV.[7,9,10] 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 2).[6] Most often PrEP is 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 3). After consistently taking daily PrEP, 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 4).[11] Future strategies may include use of a long-acting injectable antiretroviral medication, long-acting implants that slowly deliver an antiretroviral medication, or use of an antiretroviral-impregnated vaginal or cervical ring that consistently delivers antiretroviral medication to the genital mucosal surface.[12,13,14]

Guidelines for PrEP

In May 2014, the U.S. Public Health Service (USPHS) published a clinical practice guideline (Preexposure Prophylaxis for the Prevention of HIV Infection in the United States) along with a Clinical Providers' Supplement—commonly referred to as 2017 USPHS HIV PrEP Clinical Practice Guideline; in 2017, the USPHS provided updates for both of these guidelines.[11,15] Note these guidelines were last updated prior to the
2019 FDA approval of tenofovir alafenamide-emtricitabine for PrEP. The United States Preventive Services Task Force (USPSTF) has given a Grade A recommendation for the use of PrEP in groups at high risk of acquiring HIV, including men who have sex with men, persons at risk via heterosexual contact, and persons who inject drugs.[16] The USPSTF also specifically recommended use of daily tenofovir DF-emtricitabine for PrEP, but the 2019 USPSTF PrEP Recommendations were issued prior to the October 2019 FDA approval of tenofovir alafenamide-emtricitabine for PrEP.[16]
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

- **DISCOVER**: In the phase 3, randomized, double-blind, DISCOVER Trial, the safety and efficacy of daily oral tenofovir alafenamide-emtricitabine was compared with daily oral tenofovir DF-emtricitabine for HIV preexposure prophylaxis in adult men who have sex with men and adult transgender women who have sex with men.[17] The study enrolled a total of 5,387 persons in the United States and Canada, of whom only 9% were black and 1% transgender women.[17] Primary efficacy analysis at week 48 (for all participants) and week 96 (for half of participants) indicated the incidence of documented new HIV infections with daily tenofovir alafenamide-emtricitabine (0.16 per 100 person years) was noninferior to daily tenofovir DF-emtricitabine (0.34 per 100 person years) at preventing HIV acquisition in at-risk men who have sex with men and transgender women who have sex with men.[17] The overall incidence rate of HIV infection in persons enrolled in the study (0.26 per 100 person years) was markedly lower than the calculated background HIV infection rate in 2016 among men who have sex with men in the United States who were not taking PrEP (4.02 per 100 person years).[17] The tenofovir alafenamide-emtricitabine had more favorable effects on bone mineral density and biomarkers of renal safety compared to tenofovir DF-emtricitabine, but persons receiving tenofovir alafenamide had small weight gain (~1.1 kg) compared to those receiving tenofovir DF-emtricitabine (-0.1 kg) from baseline to week 48.[17]

- **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, including 29 (1%) who identified as transgender females—all of whom were considered at risk for HIV acquisition.[18] Participants were randomly assigned to receive a daily oral dose of tenofovir DF-emtricitabine or placebo. Investigators evaluated study participants every 4 weeks with 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.[18] 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.[19]

- **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 who have unprotected anal sex with men.[20] Participants were evaluated at weeks 4 and 8, and then every 8 weeks thereafter, and at each visit all participants received a comprehensive package of risk reduction interventions. Adherence was measured by pill count, structured interviews, and, in some participants, 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.[20]

- **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 that evaluated the efficacy of daily oral tenofovir DF-emtricitabine for the prevention of HIV among sexually active men without HIV who reported unprotected anal sex with men in the previous 90 days.[21] 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%. [21]

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-serodifferent 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. [22] The partners with HIV 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 that existed at the time the study was conducted). [22] 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 acquisition 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. [22] 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 had tested negative for HIV. [23] In this study, daily oral use of tenofovir DF-emtricitabine resulted in a 62% reduction in HIV acquisition when compared with placebo. [23] 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 in urban and rural South Africa. [24] The HIV serostatus, safety, sexual behavior, and gel and condom use were assessed at monthly follow-up visits for 30 months. [24] The study demonstrated that tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence. [24]

- **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. [25] Participants were seen at monthly follow-up visits, and study drug was discontinued among women who became pregnant during the trial. [25] 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. [25] Adherence was low in this trial, with detectable plasma drug levels in less than 50% of the women assigned to tenofovir DF-emtricitabine. [25]

- **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 from East Africa and South Africa. [26] Adherence estimates based on face-to-face interviews and audio computer-assisted self-interviews were high in all 3 groups (84% to 91%), but 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. The study was stopped in the group receiving oral tenofovir DF and the group receiving topical tenofovir after interim analysis determined futility. The group receiving oral tenofovir DF-emtricitabine continued to study completion, but no reduction in HIV acquisition was observed in the tenofovir DF-emtricitabine arm 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 women without HIV 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. 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).

**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. 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. 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).

**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 who inject drugs to receive either daily oral tenofovir DF or placebo. All participants also received access to addiction support services, methadone programs, bleach for cleaning needles, condoms, and primary care medical services. After a median follow-up time of 4.6 years, the relative risk reduction in HIV 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.
Persons to Consider for PrEP

The 2019 USPSTF PrEP Recommendations provide a summary of specific populations that should be considered for HIV PrEP.[16] Note these recommendations for PrEP pertain to persons who do not have HIV but are at risk of acquiring HIV. Despite clear recommendations for populations to consider for PrEP, recent surveillance data from the CDC indicate only approximately 18% of individuals at risk for HIV infection were prescribed PrEP in the United States in 2018 and the use of PrEP varied significantly among states (Figure 5).[1] The specific recommended indications for PrEP are outlined below:

Men who Have Sex with Men

- Adult man, and
- Without acute or established HIV, and
- Any male sex partners in past 6 months, and
- Not in a monogamous partnership with a recently tested, HIV-negative man

AND at least one of the following

- Any anal sex without condoms (insertive or receptive) in past 6 months
- Had a bacterial sexually transmitted infection (syphilis, gonorrhea, or chlamydia) diagnosed or reported in the past 6 months

Heterosexually Active Women and Men

- Adult person, and
- Without acute or established HIV, and
- Any type of sex with opposite sex partners in the past 6 months, and
- Not in a monogamous partnership with a recently tested, HIV-negative partner

AND at least one of the following

- Is a man who has sex with both women and men (behaviorally bisexual)
- Infrequently uses condoms during sex with one or more partners of unknown HIV status who are known to be at substantial risk of HIV (e.g. person who injects drugs or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner
- Had a bacterial sexually transmitted infection (syphilis, gonorrhea, or chlamydia) diagnosed or reported in the past 6 months

Persons who Inject Drugs

- Adult person, and
- Without acute or established HIV, and
- Any injection of drugs not prescribed by a clinician in the past 6 months

AND at least one of the following

- Any sharing of injection or drug preparation equipment in past 6 months
- Risk of sexual acquisition of HIV

Transgender Persons

- Consider in all transgender persons at risk of acquiring HIV sexually
Regimens Approved for HIV PrEP

Findings from multiple PrEP clinical trials using oral tenofovir DF-emtricitabine have demonstrated safety and a substantial reduction in the rate of HIV acquisition for men who have sex with men (MSM),[18,20,21] men and women in heterosexual HIV-serodifferent couples,[22] heterosexual men and women recruited as individuals,[23] transgender women who have sex with men,[18,20] In addition, tenofovir DF alone was shown to be safe and effective as PrEP for persons who inject drugs.[29] On the basis of these study results, the U.S. Food and Drug Administration (FDA) approved tenofovir DF-emtricitabine for PrEP in July 2012.[30] More recently, data from the phase 3 DISCOVER trial showed that tenofovir alafenamide-emtricitabine was noninferior to tenofovir DF-emtricitabine for PrEP in cisgender men who have sex with men and transgender women who have sex with men.[17] Findings from the DISCOVER trial led to the U.S. FDA approval of tenofovir alafenamide for PrEP in October 2019.[31] Thus, at this time in the United States, there are two medications approved for HIV PrEP: tenofovir DF-emtricitabine and tenofovir alafenamide-emtricitabine.

Tenofovir DF-emtricitabine

- **Indication**: Tenofovir DF-emtricitabine is indicated for PrEP to reduce the risk of sexually acquired HIV in at-risk adults and adolescents who weigh at least 35 kg. Individuals must have a negative HIV test prior to starting tenofovir DF-emtricitabine for PrEP.
- **Dosing**: Tenofovir DF-emtricitabine for HIV PrEP should be taken as one tablet once daily.
- **Formulation**: tenofovir DF-emtricitabine is a two-drug fixed-dose combination that contains 300 mg of tenofovir DF and 200 mg of emtricitabine 200 mg.
- **Food Requirements**: Take with or without food.
- **Use in Persons with Renal Impairment**: For HIV PrEP, tenofovir DF-emtricitabine is not recommended for persons who have an estimated creatinine clearance less than 60 mL/min.

Tenofovir alafenamide-emtricitabine

- **Indication**: Tenofovir alafenamide-emtricitabine is indicated for PrEP in at-risk adults and adolescents weighing at least 35 kg to reduce the risk of HIV infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex. Individuals must have a negative HIV test prior to starting tenofovir alafenamide-emtricitabine for PrEP. Tenofovir alafenamide-emtricitabine is not indicated for receptive vaginal sex because effectiveness in this population has not been evaluated. Although the PrEP indication for tenofovir alafenamide-emtricitabine does not exclude use for men at risk of sexual acquisition of HIV via insertive vaginal sex, it is important to note that tenofovir alafenamide-emtricitabine has also not been studied as a prevention measure for insertive vaginal sex.
- **Dosing**: For HIV PrEP, tenofovir alafenamide-emtricitabine should be taken as one tablet once daily. Alternative dosing, such as on-demand use is not recommended.
- **Formulation**: Tenofovir alafenamide-emtricitabine is a two-drug fixed dose combination that contains 25 mg of tenofovir alafenamide and 200 mg of emtricitabine.
- **Food Requirements**: Take with or without food.
- **Use in Persons with Renal Impairment**: For HIV PrEP, tenofovir alafenamide-emtricitabine is not recommended for persons who have an estimated creatinine clearance less than 30 mL/min.

Additional Considerations

- **Use of PrEP in Persons who Inject Drugs**: The two FDA-approved medications for PrEP (tenofovir DF-emtricitabine and tenofovir alafenamide-emtricitabine) do not have an FDA indication for preventing HIV acquisition through injection drug use. The Bangkok Tenofovir Study showed that persons who inject drugs and take daily tenofovir DF alone for PrEP experienced a significant reduction in new HIV infections compared with placebo, with this benefit of PrEP occurring for both men and women.[29] The 2017 USPHS HIV PrEP Clinical Practice Guideline and the 2019 USPSTF PrEP
Recommendations list persons who inject drugs as candidates for PrEP, with both noting persons who inject drugs may also have risk of sexual acquisition of HIV.\[11,16\] Based on available data and guidance from the USPS and USPSTF, persons who inject drugs should be considered for PrEP with daily tenofovir DF-emtricitabine.\[11,16,29\]

- **Use of PrEP in Transgender Persons:** The risk of HIV acquisition is increased among sexually active transgender persons, particularly transgender women. In the United States, approximately 25% of transgender women are living with HIV and this number increased to approximately 55% for transgender black women.\[32\] Unfortunately, there are limited PrEP data for transgender women and scarce (or no data) with PrEP for transgender men.\[33,34\] Further, the FDA indications for PrEP with tenofovir DF-emtricitabine and tenofovir alafenamide-emtricitabine do not specifically address transgender persons. Nevertheless, based on available data and extrapolation for data with cisgender persons, HIV PrEP should be considered in all transgender women and men who have an increased risk for HIV acquisition, particularly those who have anal sex. In transgender persons, tenofovir alafenamide-emtricitabine should not be used as PrEP to prevent HIV acquisition via receptive vaginal sex. In a small pharmacokinetic study, investigators reported transgender women receiving tenofovir DF-emtricitabine for PrEP concomitantly with estrogens for gender-affirming care had a modest reduction in tenofovir and emtricitabine plasma levels compared with cisgender men on the same PrEP medication.\[35\] Further research on PrEP in transgender persons is needed.

- **Use of PrEP in Periconception, Antepartum, and Postpartum Periods:** Women are at increased risk of HIV acquisition during the periconception period due to increased condomless sex, and biological factors, such as alterations in adaptive immunity, increased genital tract inflammation, and changes to the vaginal microbiome.\[36,37,38\] There are substantial data in women demonstrating the safety of tenofovir DF-emtricitabine for PrEP and for treatment of HIV during the periconception, antepartum, and postpartum periods.\[23,39,40\] The Perinatal Guidelines now strongly recommend that once daily tenofovir DF-emtricitabine should be offered as PrEP to women at high risk for HIV acquisition, regardless of whether they are trying to conceive, are pregnant, or breastfeeding.\[41\] Women should be counseled that it will take approximately 20 days after taking once daily dosing of tenofovir DF-emtricitabine for adequate protection against HIV, so alternate contraception strategies should be used in the interim. No data exist for the use of on-demand PrEP for individuals with vaginal exposure to HIV.

- **On-Demand PrEP Dosing:** 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,\[20\] there are no medications approved for use as on-demand HIV PrEP in the United States. In addition, the 2017 USPHS HIV PrEP Clinical Practice Guideline recommends against using the on-demand approach for HIV PrEP.\[11\]

- **Use of Tenofovir DF or Tenofovir Alafenamide as Single Agents for PrEP:** Although tenofovir DF alone was found to be effective in the Bangkok PrEP injection drug trial and in one trial of heterosexually active adults,\[22,29\] it is not FDA-approved as a single medication for PrEP. The 2017 USPHS HIV PrEP Clinical Practice Guideline specifically recommends against using tenofovir DF alone for PrEP, even among persons who inject drugs.\[11\] There are no data with tenofovir alafenamide alone for PrEP and the single agent tenofovir alafenamide should not be used for HIV PrEP.
Baseline Laboratory Studies

The 2017 USPHS HIV PrEP Clinical Practice Guideline recommends performing a risk assessment and baseline laboratory evaluation prior to prescribing PrEP. In order to qualify for PrEP, an individual should have substantial, ongoing risk for HIV and a baseline laboratory evaluation that includes the following:

- **HIV Testing**: Ideally, baseline HIV testing with an HIV-1/2 antigen-antibody immunoassay should be performed within 1 week of starting PrEP. Note that point-of-care tests, especially oral rapid tests, are not recommended for HIV testing prior to starting PrEP, due to the low sensitivity of these tests for diagnosing recent infection. Confirming a negative baseline HIV test prior to starting PrEP is extremely important, particularly since use of the two-drug PrEP regimen (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine) in a person with HIV infection would provide inadequate treatment of the HIV and likely result in the development of HIV drug resistance.

- **Renal Function**: A baseline serum creatinine should be ordered to evaluate renal function, including a confirmed calculated creatinine clearance using the Cockcroft-Gault formula. Persons with an estimated creatinine clearance less than 60 mL/min should not receive tenofovir DF-emtricitabine for PrEP. Similarly, persons with estimated creatinine clearance less than 30 mL/min should not receive tenofovir alafenamide-emtricitabine for PrEP.

- **Sexually Transmitted Infections**: Baseline testing for sexually transmitted infections should include serologic testing for syphilis in all, testing for gonorrhea in all sexually active adults, and testing for chlamydia in sexually active men who have sex with men.

- **Pregnancy Testing**: All women who have the potential to become pregnant should have a pregnancy test prior to starting PrEP. If the pregnancy test is positive, counseling should be offered regarding overall benefits of taking tenofovir DF-emtricitabine for PrEP during pregnancy. Global demonstration projects have established the efficacy of PrEP in preventing sexual and HIV perinatal transmission during periconception and pregnancy. In addition, recent large systematic reviews have verified the safety of tenofovir DF and emtricitabine use during pregnancy and/or lactation. Healthcare providers are encouraged to register their patients who become pregnant while on PrEP at the online Antiretroviral Pregnancy Registry. It is important to note that tenofovir alafenamide-emtricitabine is not FDA-approved for women for the prevention of HIV through vaginal sex.

- **Hepatitis B**: In a person with unknown hepatitis B status, baseline serologic screening should include hepatitis B surface antigen (HBsAg), antibody to hepatitis B core (anti-HBc), and antibody to hepatitis B surface antigen (anti-HBsAg). Persons nonimmune to hepatitis B should be offered immunization for hepatitis B. Persons with a positive HBsAg test should have further evaluation for the management of hepatitis B. Testing for hepatitis B is important because HIV PrEP medications also treat HBV and an individual with active hepatitis B infection could develop a hepatitis flare following discontinuation of the PrEP medications. Persons with active hepatitis B can receive PrEP, but, upon discontinuation of PrEP, they require close follow-up and evaluation for further management of hepatitis B infection.

- **Hepatitis C**: Baseline screening for hepatitis C infection with hepatitis C antibody should be performed for all persons starting PrEP.

- **Hepatitis A**: For men who have sex with men or persons who inject drugs who will be starting PrEP, experts recommend also obtaining baseline hepatitis A serologic studies and immunizing individuals in these groups who do not have evidence of immunity against hepatitis A virus, especially in light of recent hepatitis A outbreaks in the United States.

Immunizations

The evaluation and management of persons receiving PrEP also provides an opportunity to counsel and administer several vaccines for pathogens that may be transmitted through sex or injection drug use. Screening for hepatitis B in persons initiating PrEP will identify some persons who are nonimmune to hepatitis
B; these individuals should receive a complete hepatitis B vaccine series.\cite{47} In addition, hepatitis A immunization is recommended for certain population that may overlap with persons seeking PrEP, including MSM and persons who inject drugs.\cite{46,47} Persons seeking PrEP who have not received the human papillomavirus (HPV) vaccine and are candidates (based on their age) for this vaccine should receive immunization with the 9-valent HPV vaccine.\cite{47,48}

**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.\cite{11} When PrEP is prescribed, clinicians should provide access, directly or by facilitated referral, to proven effective risk-reduction and support services (Table 1).\cite{11} In addition, it is important that persons who inject drugs understand that taking tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine does not reduce the risk of hepatitis C acquisition.
Time to Achieve Protection after Initiating PrEP

After initiating PrEP with tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, these medications must reach the body tissues and then undergo phosphorylation to function as an inhibitor of HIV replication. Available data in humans suggest that with oral ingestion of tenofovir DF, the 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.[49,50,51] The time to reach adequate concentrations for the purposes of HIV prevention remains unknown, but is likely significantly shorter than the time to reach maximal concentrations. The 2017 USPHS HIV PrEP Clinical Practice Guideline does not provide a specific recommendation for the time needed for tenofovir DF-emtricitabine to reach adequate tissue levels to achieve protection from HIV infection.[11] The 2018 IAS-USA HIV Treatment and Prevention Recommendations suggest using a 7-day lead-in time with daily dosing of tenofovir DF-emtricitabine for rectal, penile, and vaginal exposures to ensure adequate tissue levels are achieved.[52] Pharmacologic studies of tenofovir alafenamide-emtricitabine are underway. Accordingly, there are no official recommendations regarding how long it would take to achieve protection against HIV acquisition after initiating tenofovir alafenamide-emtricitabine for PrEP.
Monitoring on PrEP

All individuals taking tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine for PrEP should have a number of laboratory studies obtained as part of their 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 2017 USPHS HIV PrEP Clinical Practice Guideline recommends the following regarding laboratory monitoring for persons taking tenofovir DF-emtricitabine for PrEP ([Figure 6]):[11] Note the laboratory monitoring guidance was issued prior to the approval of tenofovir alafenamide-emtricitabine for PrEP, but the recommendations listed below for persons taking tenofovir DF-emtricitabine can also be followed for persons taking tenofovir alafenamide-emtricitabine.

- **HIV Testing**: Repeat HIV testing and evaluation for signs and symptoms of acute HIV infection should be performed at least every 3 months ([Table 2]).[11,53] If, at any point, the individual taking PrEP has a confirmed new diagnosis of HIV, further evaluation should occur via baseline laboratory studies (including an HIV drug resistance genotype), and the person newly diagnosed with HIV should promptly have the PrEP regimen converted to a fully suppressive HIV antiretroviral treatment regimen.

- **Pregnancy Testing**: For women who might become pregnant while taking PrEP, pregnancy testing 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 woman and her prenatal medical provider about the risks and benefits of continuing PrEP during pregnancy. Significant experience now exists with the use of tenofovir DF-emtricitabine as a component of antiretroviral therapy for women with HIV who are pregnant and the data suggest no safety concerns.[54]

- **Monitoring Renal Function**: Monitoring for renal function should be performed at least every 6 months in persons receiving tenofovir DF-emtricitabine for PrEP and should include a serum creatinine test with an estimation of creatinine clearance.[11] There are no guidelines for the frequency of monitoring of renal function in persons receiving tenofovir alafenamide-emtricitabine for PrEP.

- **Sexually Transmitted Infections (STIs)**: For MSM receiving PrEP, screening for bacterial STIs (chlamydia, gonorrhea, and syphilis) should occur at least every 3 months.[11] For other sexually active adolescents and adults receiving PrEP, screening for STIs is recommended at least every 6 months.[11] Although STI screening in transgender persons on PrEP is not addressed in this guidance, many experts would recommend every 3-month STI screening for transgender persons on PrEP. Screening for chlamydia and gonorrhea should include all appropriate body sites based on reported sexual activity.

- **Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV)**: The monitoring guideline does not include a recommendation to repeat HBV or HCV testing while a person is taking PrEP. Some experts recommend annual testing for HCV based on sexual and drug use practices, especially for MMS. Individuals tested at baseline who were nonimmune to HBV should receive vaccination against hepatitis B, unless they have evidence of active hepatitis B infection.
Acquisition of HIV While on PrEP

If HIV acquisition is documented to occur while an individual is taking either tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine for PrEP, then a number of subsequent steps should occur.\[11\]

- 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).
- If the clinician prescribing PrEP is not experienced with HIV management and antiretroviral therapy, then the person newly diagnosed with HIV should receive a referral to a medical provider who has significant HIV clinical expertise.
- Partner notification should occur with all persons newly diagnosed with HIV.
- Once a diagnosis of HIV is made, it is important the person have the two-drug PrEP regimen (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine) modified to a fully suppressive antiretroviral regimen. In this setting, most experts would immediately switch to a fully suppressive antiretroviral regimen and modify the regimen, if needed, when the results from the genotype become available.
Impact of Adherence on Efficacy of PrEP

In the PrEP trials completed to date, adherence to PrEP has been the single most important factor that impacts efficacy.\cite{6,55,56} 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 7).\cite{18} In the Partners PrEP trial, there was an overall 75% relative reduction in HIV acquisition for persons who received tenofovir DF-emtricitabine compared with those who received placebo; among participants receiving tenofovir DF-emtricitabine who had a detectable blood level of tenofovir (a marker of adherence) there was a 90% reduction in HIV acquisition compared with those with an undetectable tenofovir level.\cite{22}

With 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 8).\cite{57} 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.\cite{25,55} 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).\cite{11} Additional data are pending from the DISCOVER trial that correlate adherence with HIV risk reduction when using tenofovir alafenamide-emtricitabine or tenofovir DF-emtricitabine for PrEP.
PrEP and Development of HIV Drug Resistance

Incidence of HIV Drug Resistance in Persons Taking PrEP

Although development of drug resistance is a concern in an individual who acquires HIV infection while taking tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, in the large PrEP trials involving tenofovir DF-emtricitabine investigators have reported a low incidence of HIV resistance.[22, 58, 59] There are no reported data that have evaluated HIV drug resistance in persons who acquired HIV while taking tenofovir alafenamide-emtricitabine for PrEP. 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.[59] 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.[58]

Development of Breakthrough HIV Drug Resistance

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, this more recent analysis confirms that PrEP–associated drug resistance mutations can occur in association with PrEP breakthrough infections (i.e. person acquires HIV while taking PrEP).[22, 58] In addition, transmission of multi-drug resistant HIV has occurred.[60] Nonetheless, based on available data, PrEP-related HIV drug resistance is thought to be low as long as HIV infection is recognized promptly and PrEP is modified to a fully suppressive antiretroviral regimen immediately upon detection of HIV.

Evaluation for Suspected HIV Drug Resistance

An HIV RNA level and an HIV genotype resistance assay should be ordered promptly for any person taking PrEP who is diagnosed with HIV. In some instances, however, individuals who acquire HIV while taking 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 or tenofovir alafenamide-emtricitabine.

Monitoring for HIV Infection to Prevent Resistance

To minimize the risk of developing resistance among persons taking PrEP, the 2017 USPHS HIV PrEP Clinical Practice Guideline 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.[11]
Adverse Effects of Medications Used for PrEP

Adverse Effects with 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.\[7,11\] 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.\[61,62,63\] Nevertheless, extensive treatment experience with tenofovir DF when used as treatment for persons with HIV infection has shown the potential for tenofovir DF to cause nephrotoxicity.

Monitoring Renal Function and Bone Mineral Density

Accordingly, the 2017 USPHS HIV PrEP Clinical Practice Guideline recommends careful monitoring of renal function in all patients taking tenofovir DF-emtricitabine for PrEP.\[11\] 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.\[64,65,66,67\] Findings from a recent study suggested the minor losses in bone mineral density that occurred in persons receiving PrEP were recovered within 12 to 18 months after stopping PrEP.\[68\] Although tenofovir DF could potentially impact bone density, routine baseline (or follow-up) bone density scanning is not recommended.

Adverse Effects with Tenofovir alafenamide-Emtricitabine

Preliminary results from the DISCOVER trial that compared once-daily dosing of tenofovir alafenamide-emtricitabine to once-daily tenofovir DF-emtricitabine for PrEP demonstrated that tenofovir alafenamide-emtricitabine was well tolerated and safe, had very low rates of adverse event discontinuations, and had better bone and renal safety outcomes than tenofovir DF-emtricitabine.\[17\] Gastrointestinal symptoms were the most commonly reported adverse events associated with the use of tenofovir alafenamide-emtricitabine as PrEP.\[17\]
Changes in Sexual Practices Among Persons Receiving PrEP

Critics of PrEP have argued that its use will lead to behavioral disinhibition and an increase in higher risk sexual and drug use practices, an effect labeled risk compensation.[69,70] The evidence in PrEP clinical trials for risk compensation in the setting of PrEP use has been mixed.[6,69,70,71,72,73] In addition, clinical experience suggests risk behaviors in the community setting may not parallel those in PrEP clinical trials, since individuals are likely to receive more extensive and frequent counseling for HIV prevention measures in these trials. Regardless, most experts believe the HIV prevention value of PrEP outweighs any potential change in sexual practices that may occur while persons are receiving PrEP. The following summarizes key findings in major PrEP studies that have examined the impact of PrEP on sexual activity and rates of sexually transmitted infections.

- **I-PrEx**: 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 infection (Figure 9).[69]
- **Partners PrEP**: 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.[22] 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.[23]
- **Bangkok Tenofovir**: In the PrEP trial of persons who inject drugs in Thailand, rates of injecting drugs and sharing needles decreased at follow-up.[29]
- **Victorian PrEP Demonstration Project**: 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.[74]
- **PrEPX Study**: The Preexposure Prophylaxis Expanded study, which was a multi-site, open-label intervention study in Australia, with more than 4,000 participants enrolled, reported a higher incidence of bacterial sexually transmitted infections in gay and bisexual men after study enrollment to receive PrEP (compared to preenrollment), particularly among young gay and bisexual men who had a greater number of sex partners.[71]
**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. Several key factors should be taken into consideration at the time of discontinuing PrEP:

- Upon discontinuation of PrEP, the 2017 USPHS HIV PrEP Clinical Practice Guideline recommends that repeat HIV testing should always be performed and the reason for discontinuing PrEP should be documented in the health record. 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 an individual 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 to start a fully suppressive antiretroviral treatment regimen.
- If an individual with chronic hepatitis B infection is taking tenofovir DF-emtricitabine or tenofovir alafenamide for PrEP, discontinuing the medication could lead to a hepatitis B flare since HBV DNA levels can dramatically rebound. Accordingly, for persons with chronic hepatitis B infection who will no longer be taking PrEP, continued hepatitis B treatment may be necessary.
Transitioning from Nonoccupational PEP to PrEP

Indications for Transition from Nonoccupational PEP to PrEP

There are three circumstances that warrant the administration of nonoccupational postexposure prophylaxis (PEP) followed by a transition to PrEP:[11, 15, 75, 76]

1. An individual starts on a nonoccupational PEP antiretroviral regimen sexual or injection-related exposure to HIV and during the evaluation (or follow-up) it becomes evident they will likely have significant and ongoing risk of acquiring HIV after they complete the 28-day PEP course; or
2. A person has received repeated courses of nonoccupational PEP and it is determined that regular use of PrEP would be a more effective HIV prevention strategy; or
3. A person is evaluated to start PrEP and during the evaluation they report a significant HIV risk exposure within the past 72 hours.

Timing of the Transition from Nonoccupational PEP to PrEP

The practical implementation of this transition from nonoccupational PEP to PrEP is addressed in the Clinical Provider’s Supplement of the 2017 USPHS HIV PrEP Clinical Practice Guideline.[15] This guidance provides two options for this transition: immediate transition to PrEP at the end of the 28-day course or defer the initiating of PrEP until a later time.[15]

Immediate Transition from Nonoccupational PEP to PrEP

Many experts now recommend that if HIV exposures are not isolated, and the person seeking nonoccupational PEP is interested in taking PrEP, then the clinician should consider beginning PrEP immediately upon completing the 28-day nonoccupational PEP regimen.[11, 15, 76] For some individuals, the immediate transition from taking nonoccupational PEP and initiating PrEP may be particularly important if they have ongoing or imminent significant risk for acquiring HIV. In this situation, requiring a gap period prior to starting PrEP to exclude HIV from the prior exposure could result in a significant risk of acquiring HIV while off all antiretroviral medications. The major concern with immediate transition to PrEP is that an individual could acquire HIV from the exposure that warranted nonoccupational PEP (a three-drug regimen) and the transition to PrEP (a two-drug regimen) would result in partial treatment of HIV, with probable development of HIV drug resistance. This risk, however, appears to be very low. The Clinical Provider’s Supplement in the 2017 USPHS HIV PrEP Clinical Practice Guideline recommends the following when immediately transitioning an individual from nonoccupational PEP to PrEP.[15]

After the individual taking nonoccupational PEP completes 28 days of nonoccupational PEP:

- Repeat a rapid HIV test (ideally with an HIV-1/2 antigen-antibody immunoassay) and assess for signs and symptoms of acute HIV infection.  
  Author’s note: we recommend including a slightly different option whereby a person taking nonoccupational PEP could undergo HIV testing with the more sensitive laboratory-based HIV-1/2 antigen-antibody immunoassay, with the test performed several days prior to completing of the 28-day course, making sure this is arranged to ensure the result will be known prior to the end of the 28-day nonoccupational PEP course.
- If the HIV test is positive or suspicion exists of possible acute HIV infection, draw blood for confirmatory testing and continue the 3-drug nonoccupational PEP regimen should be extended past the 28-days pending confirmation of HIV status.
- If HIV infection is confirmed, the individual will need prompt evaluation for the management of newly acquired HIV.
- If the HIV testing is negative and no signs or symptoms of acute infection exist:
  - Stop the third medication in the nonoccupational PEP regimen (usually raltegravir or
dolutegravir) and continue tenofovir DF-emtricitabine as the 2-drug PrEP regimen. 

Author’s note: With the recent FDA approval of tenofovir alafenamide-emtricitabine for PrEP this provides an additional option to consider when transitioning from nonoccupational PEP to PrEP. Since tenofovir alafenamide-emtricitabine is not recommended for nonoccupational PEP, a transition to the 3-drug nonoccupational PEP regimen, which typically utilizes tenofovir DF-emtricitabine, to the 2-drug tenofovir alafenamide-emtricitabine for PrEP would require switching the entire regimen. Tenofovir alafenamide-emtricitabine is not indicated for for PrEP in women to prevent acquisition of HIV via receptive vaginal sex.

- Complete any PrEP baseline laboratory testing not already performed for the nonoccupational evaluation and/or follow-up.
- Provide PrEP medication adherence and risk-reduction support counseling.
- Complete any insurance/medication assistance paperwork required to cover PrEP medications, since the medication coverage might be different from the coverage required for nonoccupational PEP. Provide a 90-day supply of the PrEP medication.
- Schedule follow-up visits for HIV, sexually transmitted infections, and other laboratory testing as well as medication refills on the basis of standard PrEP clinical practice guidelines recommendations.

Deferred Initiation of PrEP

Some person receiving nonoccupational PEP, who are PrEP candidates, prefer to defer the initiation of PrEP. This desire or need to defer PrEP may result from a personal preference, a strong wish from the patient or clinician to definitely exclude HIV prior to starting PrEP, or issues related to getting PrEP medications paid for via insurance (or accessed through a patient assistance program). To definitely exclude HIV after the exposure related to taking nonoccupational PEP would typically take approximately 12 weeks if using a laboratory-based HIV-1/2 antigen-antibody immunoassay.[77] In this situation, some experts advocate for HIV RNA testing several weeks after completing nonoccupational PEP, particularly if there is a more urgent need to prescribe PrEP. If HIV PrEP is deferred the Clinical Provider’s Supplement in the 2017 USPHS HIV PrEP Clinical Practice Guideline recommends including the following in the subsequent approach:[15]

- Reinforce the critical nature of safer sexual or injection drug use strategies while pending PrEP initiation
- Initiate PrEP, when possible
- Obtain baseline testing per PrEP guidelines prior to initiating PrEP
Racial and Gender Disparities in PrEP Use

Despite the overwhelming evidence favoring PrEP use for HIV prevention, there are substantial data demonstrating low rates of PrEP uptake and/or high rates of PrEP discontinuation in certain demographic groups, particularly (1) Black and Hispanic men who have sex with men or (2) women at risk for HIV.[1,2,78,79,80,81,82]

- **PrEP Uptake by Gender**: Recent surveillance data from the CDC indicate that among persons at risk for acquiring HIV in 2018, men had three times higher HIV PrEP coverage compared to cisgender women, with only approximately 7% of cisgender women who could benefit from PrEP were prescribed PrEP.\[^{[1]}\] Moreover, the recent DISCOVER PrEP trial that evaluated tenofovir alafenamide-emtricitabine for PrEP excluded cis-gender women—further contributing to the gender disparities for the use of PrEP in the United States.\[^{[17]}\] A large study in the United States that evaluated HIV-seronegative, nonpregnant women who were 15 to 64 years of age found that PrEP prescription rates were less than 0.5% for women who underwent HIV testing for HIV.\[^{[83]}\] In this same study, the investigators also reported that PrEP was not prescribed for more than 13,000 women who were diagnosed with gonorrhea or syphilis.\[^{[83]}\] Further, in a separate brief research report that discussed trends in PrEP prescription for persons with commercial insurance in the United States found that 96% of individuals taking PrEP were men, underscoring the gender disparities in the PrEP continuum of care.\[^{[84]}\] Of note, this study did not include analysis of uninsured or underinsured individuals, including sexual or gender minority persons, who are at high risk of HIV transmission.\[^{[84]}\]

- **PrEP Update by Race**: Among persons at risk for acquiring HIV, whites were seven times more likely to be on PrEP than blacks and 4 times more likely than Hispanics.\[^{[1]}\] In order to implement effective biomedical prevention strategies, there is a critical need for research into structural and behavioral factors that affect HIV risk perception and PrEP continuum of care in these vulnerable populations.
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.[85,86,87,88,89] 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.[6] Information regarding PrEP studies can be found on the PrEP Watch resource from the AIDS Vaccine Advisory Council (AVAC).
Summary Points

- Antiretroviral PrEP has been shown to be a safe and effective HIV prevention option for individuals at substantial risk of acquiring HIV.
- The FDA-approved and recommended HIV PrEP regimens are tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, with both approved for daily dosing on a regular basis.
- Tenofovir DF-emtricitabine is indicated for HIV PrEP in all adults and adolescents (who weigh at least 35 kg) who are at risk of acquiring HIV.
- Tenofovir alafenamide-emtricitabine is indicated as HIV PrEP for at-risk adults and adolescents (who weigh at least 35 kg) to reduce the risk of acquiring HIV from sex, excluding use by women to prevent HIV acquisition via receptive vaginal sex.
- A risk assessment and baseline laboratory evaluation is required prior to prescribing PrEP, including documentation that the person to receive PrEP has a negative baseline HIV test.
- 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 shows a negative HIV test result and medication adherence has been assessed.
- Monitoring for persons receiving PrEP should include HIV testing every 3 months, screening for sexually transmitted infections at least every 3 to 6 months, and renal function every 3 to 6 months.
- For HIV serodifferent 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.
- The risk for developing HIV drug resistance associated with PrEP use appears to be low, as long as HIV infection is recognized promptly and the PrEP regimen is converted to a fully suppressive antiretroviral treatment regimen.
- If an individual with chronic hepatitis B infection is taking PrEP, discontinuing tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine could lead to a serious hepatitis B flare.
- Transitioning for nonoccupational PEP to PrEP optimally involves an immediate transition, without a gap.
- When discontinuing PrEP, repeat HIV testing should always be performed and the reason for discontinuation should be documented in the health record.
Citations


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[CDC]

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[PubMed Abstract]


31. U.S. Food and Drug Administration. FDA approves second drug to prevent HIV infection as part of ongoing efforts to end the HIV epidemic. October 3, 2019 [U.S. FDA]


47. Advisory Committee on Immunization Practices (ACIP). Recommended Immunization Schedule for Ages 19 Years or Older, United States, 2021. [ACIP] -

48. Advisory Committee on Immunization Practices (ACIP). Recommended Child and Adolescent Immunization Schedule for Ages 18 Years or Younger, United States, 2021. [ACIP] -


References


Figures

Figure 1 Estimated HIV Incidence in United States, 2010-2016

Investigators from the Centers for Disease Control and Prevention incorporated data from the HIV case surveillance system and CD4 cell count test results to estimate the HIV incidence in the United States.

Figure 2 Basic Concept of Preexposure Prophylaxis

The principle of preexposure prophylaxis, as recommended in the United States, is to take an antiretroviral medication on a regular and consistent schedule (daily) to provide protection against any subsequent exposure to HIV. For this example, the antiretroviral medication would consist of daily dosing with either tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine.

Illustration by David H. Spach, MD
Figure 3 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface (Image Series) - Image 3A: Normal Genital Mucosal Surface

Illustration by David H. Spach, MD
Figure 3 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface
Image 3B: HIV Contact with Genital Mucosal Surface Following Sexual Contact

Submucosal cells that play a role in early HIV infection include CD4 T-lymphocytes, dendritic cells, and macrophages.

Illustration by David H. Spach, MD
Figure 3 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface

Image 3C: HIV Infecting Susceptible Cell in Submucosal Region

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
Figure 3 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface
Image 3D: Early Propagation of HIV in Genital Submucosal Tissue

Once cellular infection with HIV takes place, rapid HIV replication and spread to adjacent cells can occur.

Illustration by David H. Spach, MD
Figure 4 (Image Series) - Preexposure Prophylaxis and Prevention of Sexual Transmission of HIV

Image 4A: Intracellular Concentrations of Tenofovir and Emtricitabine after 1-2 Days

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 4 (Image Series) - Preexposure Prophylaxis and Prevention of Sexual Transmission of HIV
Image 4B: 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
Figure 4 (Image Series) - Preexposure Prophylaxis and Prevention of Sexual Transmission of HIV
Image 4C: Tenofovir and Emtricitabine Blocking HIV Replication

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.

Illustration by David H. Spach, MD
Figure 5 PrEP Coverage, by State, United States, 2018

For this figure, PrEP coverage is represented as a percentage and calculated by the number of persons prescribed PrEP (n = 219,691 in 2018) divided by estimated number of persons with indications for PrEP (n = 1,211,777 in 2017).

**Figure 6 Recommended Laboratory Monitoring for Persons Receiving Preexposure Prophylaxis**


<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Baseline</th>
<th>At least every 3 months</th>
<th>At least every 6 months</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
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<td>HIV screening assay</td>
<td></td>
<td>✓</td>
<td></td>
<td>Consider need for HIV RNA PCR</td>
</tr>
<tr>
<td>HBV (panel) and HCV antibody</td>
<td></td>
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<td>Offer HBV vaccination if not immune</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td></td>
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<td>✓</td>
<td>^CrCl decrease may require stopping PrEP</td>
</tr>
<tr>
<td>STI testing</td>
<td></td>
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<td>✓</td>
<td>Include oral/rectal screen for MSM if risk</td>
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<tr>
<td>Pregnancy test for women*</td>
<td></td>
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<td>✓</td>
<td>Safety of PrEP in pregnancy not known</td>
</tr>
</tbody>
</table>

Abbreviations: eCrCl = estimated creatinine clearance; STI = sexually transmitted infections

*Includes HBsAg, anti-HBc, and anti-HBs

^Do not start tenofovir DF-emtricitabine if CrCl <60 mL/min; do not start tenofovir alafenamide-emtricitabine if CrCl <30 mL/min

*For women who may become pregnant
**Figure 7 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.

Figure 8 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 9 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.

Table 1. **USPHS: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2017**

**Key Components of Behavioral Risk-Reduction Counseling**

<table>
<thead>
<tr>
<th>Establish trust and 2-way communication</th>
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<tbody>
<tr>
<td><strong>Provide feedback on HIV risk factors identified during sexual and substance use history taking</strong></td>
<td></td>
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<tr>
<td>- Elicit barriers to, and facilitators of, consistent condom use</td>
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<tr>
<td>- Elicit barriers to, and facilitators of, reducing substance abuse</td>
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<td><strong>Support risk-reduction efforts</strong></td>
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<td>- Assist patient to identify 1 or 2 feasible, acceptable, incremental steps toward risk reduction</td>
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<tr>
<td>- Identify and address anticipated barriers to accomplishing planned actions to reduce risk</td>
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<tr>
<td><strong>Monitor behavioral adherence in a nonjudgmental manner</strong></td>
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<tr>
<td>- Acknowledge the effort required for behavior change</td>
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<tr>
<td>- Reinforce success</td>
<td></td>
</tr>
<tr>
<td>- If not fully successful, assess factors interfering with completion of planned actions and assist patient to identify next steps</td>
<td></td>
</tr>
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</table>

Source:

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<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>
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<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:
Table 3. **USPHS: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States**

### Key Components of PrEP 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 effects</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 nonjudgmental 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:
