HIV 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 remained greater than 30,000 new infections per year (Figure 1). 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 (MSM), particularly in the South. It is clear that additional efforts are needed to reduce the number of new HIV infections in the United States. The risk of an individual acquiring HIV may fluctuate between periods of high sexual or drug risk activity and periods of low or no risk. Thus, HIV prevention strategies must offer options that are tailored to an individual’s needs.

An expanding number of HIV prevention methods are being implemented worldwide and HIV preexposure prophylaxis (PrEP) is now accepted as an important prevention strategy. The expanded use of HIV PrEP is a major component in the national initiative—Ending the HIV Epidemic: A Plan for the United States.

Principles of HIV 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 perinatal transmission of HIV. Most often, HIV 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 2). After consistently taking oral daily HIV PrEP or receiving regular injections of cabotegravir, the cells near the genital mucosal surface achieve high intracellular concentrations of the active components of the antiretroviral medications and thereby block replication of HIV following sexual contact with a person who has HIV (Figure 3). There are now three fundamental types of HIV PrEP available in the United States for use to prevent sexual acquisition of HIV: (1) daily PrEP with either oral tenofovir DF-emtricitabine or oral tenofovir alafenamide-emtricitabine (Figure 4), (2) on-demand, intermittent PrEP with “2-1-1” dosing using oral tenofovir DF-emtricitabine (Figure 5), and (3) use of long-acting injectable PrEP (using cabotegravir) administered every 2 months (Figure 6).

Guidelines for PrEP

- Centers for Disease Control and Prevention (CDC): In December 2021, the Centers for Disease Control and Prevention (CDC) and the U.S. Public Health Service (USPHS) published an updated 2021 CDC PrEP Clinical Practice Guideline along with an updated Clinical Providers’ Supplement. These guidelines were released just prior to the late December 2021 U.S. Food and Drug Administration (FDA) approval of long-acting injectable cabotegravir for HIV PrEP, but these new
guidelines do incorporate discussion of long-acting injectable cabotegravir into PrEP options.[9,10]

- **International Antiviral Society-USA (IAS-USA):** The International Antiviral Society-USA Panel (IAS-USA) updated their Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults guidelines in December 2022.[11] These guidelines also provide recommendations for prescribing PrEP, including oral options and injectable cabotegravir, and have recommendations for the baseline laboratory evaluation and laboratory monitoring.[11]

- **United States Preventive Services Task Force (USPSTF):** 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 MSM, people at risk via heterosexual contact, and people who inject drugs.[12] The USPSTF also specifically recommended use of daily tenofovir DF-emtricitabine for PrEP, but the 2019 USPSTF PrEP Recommendations were issued prior to the FDA approval of tenofovir alafenamide-emtricitabine for HIV PrEP and prior to the FDA approval for long-acting injectable cabotegravir for HIV PrEP.[12] The USPSTF HIV PrEP recommendations are currently under revision and the Draft Recommendations were issued on December 13, 2022.
Persons to Consider for HIV PrEP

In the United States, it is estimated that approximately 1.2 million persons have an HIV PrEP indication.\cite{9,13} Although use of HIV PrEP has increased in the United States in recent years, data from 2022 indicate that only 26% of individuals in the United States with an HIV PrEP indication were prescribed PrEP (Figure 7).\cite{14,15} In addition, significant disparities in access and receipt of HIV PrEP persist based on socioeconomic and demographic factors, such as region of residence, sex, gender, age, race, ethnicity, insurance status, residing in a state with expanded Medicaid or an HIV PrEP drug assistance program, as well as other factors. Health care professionals should provide all sexually active adult and adolescent persons with information regarding HIV PrEP.\cite{9} A brief sexual history is recommended to assess the risk of acquiring HIV and potential indications for HIV PrEP. The specific indications for HIV PrEP, as recommended in the 2021 CDC PrEP Clinical Practice Guideline, are outlined as follows:

**Sexually Active Adults and Adolescents who Weigh at Least 35 kg**

Anal or vaginal sex in past 6 months AND any of the following:

- Sex partner with HIV (especially if the person with HIV has an unknown or detectable viral load)

- Bacterial sexually transmitted infection within the past 6 months (gonorrhea, chlamydia, and syphilis for MSM and transgender women who have sex with men, including those who inject drugs; gonorrhea and syphilis for heterosexual women and men including persons who inject drugs)

- History of inconsistent or no condom use with sexual partner(s)

**Persons who Inject Drugs**

Persons who inject drugs should also be assessed for their sexual risk of HIV.

- Injecting partner who has HIV,

  or

- Sharing injection equipment

  or

- Have sexual risk for acquiring HIV
Recommended Regimens and Dosing for HIV PrEP

Currently, in the United States, there are three medications that have received FDA approval for HIV PrEP: tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine, and long-acting injectable cabotegravir. Long-acting injectable cabotegravir was shown to be superior to tenofovir DF-emtricitabine in two studies (1) in MSM and transgender women and (2) in cisgender women.[16,17] No trials have adequately evaluated the effectiveness of HIV PrEP as a prevention measure for receptive vaginal sex in transgender women who have a neovagina. In addition, no trials with any medication have specifically recruited or included transgender men, but there is no reason to think that HIV PrEP would be ineffective for transgender men.

Tenofovir DF-emtricitabine

- **Data:** Findings from multiple, randomized clinical trials using oral tenofovir DF-emtricitabine as HIV PrEP have demonstrated safety and a substantial reduction in the rate of HIV acquisition for MSM,[18,19,20] cisgender men and women in heterosexual HIV-serodifferent couples (one person has HIV and the other does not),[21] cisgender heterosexual men and women recruited as individuals,[22] and 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.[23]
- **FDA Approval and Indication for HIV PrEP:** In July 2012, the FDA approved tenofovir DF-emtricitabine for HIV PrEP.[24] Tenofovir DF-emtricitabine is indicated for HIV PrEP to reduce the risk of sexually-acquired HIV in at-risk adults and adolescents (weighing at least 35 kg) who are at risk of acquiring HIV. Individuals must have a negative HIV test prior to starting tenofovir DF-emtricitabine for PrEP.
- **Dosing:** The recommended dosing of tenofovir DF-emtricitabine when use for HIV PrEP is one tablet once daily. Alternative dosing, such as on-demand (2-2-1) dosing, is not included in the FDA indication, but can be considered “off-label” for select MSM, per CDC Guidelines.
- **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:** Tenofovir DF-emtricitabine is not recommended for HIV PrEP in persons who have an estimated creatinine clearance of less than 60 mL/min.

Tenofovir alafenamide-emtricitabine

- **Data:** In the phase 3 DISCOVER trial, tenofovir alafenamide-emtricitabine was noninferior to tenofovir DF-emtricitabine as HIV PrEP for cisgender men who have sex with men and transgender women who have sex with men.[25]
- **FDA Approval and Indication for HIV PrEP:** In October 2019, the FDA approved tenofovir alafenamide-emtricitabine for HIV PrEP in adults and adolescents (weighing at least 35 kg) who are at risk of acquiring HIV from sexual acquisition, excluding individuals at risk from receptive vaginal sex.[26] 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 established, although it is currently under investigation. In addition, tenofovir alafenamide-emtricitabine as HIV PrEP has not yet been adequately studied using on demand (2-1-1) dosing, or in people who are risk of acquiring HIV from injecting drugs. Further, 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 has not been studied as a prevention measure for this indication.
- **Dosing:** For HIV PrEP, tenofovir alafenamide-emtricitabine should be taken as one tablet once daily. Alternative dosing, such as on-demand (2-1-1) dosing, 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, unless they are on dialysis. For those on dialysis, tenofovir alafenamide-emtricitabine can be given after dialysis on dialysis days.

Long-Acting Injectable Cabotegravir

- FDA Approval and Indication for HIV PrEP: In December 2021, the FDA approved long-acting injectable cabotegravir as HIV PrEP for at-risk adults and adolescents (weighing at least 35 kg) who are at risk of sexual acquisition of HIV. Long-acting cabotegravir has not been studied as a prevention measure for people who are risk of acquiring HIV from injecting drugs.
- Dosing: Long-acting injectable cabotegravir is given as a 600 mg (3 mL) injection, which is repeated 1 month after the first injection, and then repeated every 2 months thereafter. An optional oral lead-in with cabotegravir 30 mg once daily may be used for approximately 1 month to assess the tolerability of cabotegravir. If the oral cabotegravir lead-in is used, the first injection of cabotegravir should be given on the last day of the oral lead-in (or within 3 days of completing the oral lead-in).
- Formulation: Cabotegravir is available as a 200 mg/mL solution and is administered as a 3 mL intramuscular injection in the gluteal region. Oral cabotegravir is a 30 mg tablet that is taken once daily.
- Food Requirements: Long-acting injectable cabotegravir has no food restrictions. Oral cabotegravir can be taken with or without food.
- Use in Persons with Renal Impairment: For HIV PrEP, cabotegravir has no renal restrictions. For persons who have a creatinine clearance less than 30 mL/min, increased monitoring for cabotegravir toxicity is recommended. The monitoring should consist of testing hepatic aminotransferase levels because of potential hepatotoxicity. Hemodialysis is not expected to impact cabotegravir levels.

On-Demand (2-1-1) HIV PrEP

- Setting for Using On-Demand (2-1-1) HIV PrEP: The use of on-demand PrEP (also called non-daily, intermittent, event-driven, or 2-1-1), which consists of taking tenofovir DF-emtricitabine before and after sex, was shown to be highly efficacious at preventing HIV in MSM in the large IPERGAY trial.[20] Although there are no medications approved for use as on-demand (2-1-1) HIV PrEP in the United States, the 2021 CDC PrEP Clinical Practice Guideline recommend that on-demand (2-1-1) HIV PrEP with oral tenofovir DF-emtricitabine can be considered in selected adult MSM who meet certain criteria.[9] Specifically, this may be an appropriate dosing option for MSM who have sex infrequently (less than once per week), who tend to anticipate sex, and who prefer the intermittent dosing option to daily HIV PrEP. A person who starts on-demand HIV PrEP then decides they prefer daily dosing or who starts to have sex more frequently can change to daily dosing or to injectable cabotegravir. For MSM using demand (2-1-1) dosing, clinicians should provide counseling about the importance of taking the doses as recommended for every sexual encounter and about the importance of continuing to have follow-up HIV and STI testing. On-demand PrEP should not be used for persons with chronic hepatitis B infection.

- Dosing with On-Demand (2-1-1) HIV PrEP: With on-demand (2-1-1) HIV PrEP, dosing 2 pills of tenofovir DF-emtricitabine are taken 2 to 24 hours prior to sex, 1 pill is taken 24 hours after the initial 2 pills, and 1 pill is taken 48 hours after the initial 2 pills. If sexual activity occurs on the day after completing the 2-1-1 dosing, 1 pill a day should continue to be taken for 48 hours after the last sexual event.[9] If a gap of less than 7 days occurs prior to the next sexual event, then 1 pill daily of tenofovir-DF should be resumed and continued for 48 hours after the last sexual event.[9] If a gap of 7 days or more occurs before the next sexual event, then the PrEP dosing should start over again with the 2-1-1 dosing.[9] For MSM using demand (2-1-1) dosing, clinicians should provide counseling about the importance of taking the doses as recommended for every sexual encounter and about the importance of continuing to have follow-up HIV and STI testing. On-demand PrEP should not be used for persons with chronic hepatitis B infection.

Additional Considerations

- HIV PrEP for Persons who Inject Drugs: Although no medications has an FDA indication for
HIV PrEP for Transgender Persons: The overall 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 increases to approximately 55% for transgender Black women. Some HIV PrEP trials have included transgender women, such as the iPrEX trial of oral daily tenofovir DF-emtricitabine and the HPTN 083 trial of long acting injectable cabotegravir, but the number of transgender women who enrolled in both studies was small. Further, there are no published data from clinical trials on the efficacy of HIV PrEP for transgender men. Nevertheless, based on available data and extrapolation of data with cisgender persons, HIV PrEP should be considered for all transgender women and transgender men who have a substantial risk of HIV acquisition. For transgender persons, tenofovir alafenamide-emtricitabine should not be used as PrEP to prevent HIV acquisition via receptive vaginal sex. Data regarding the impact of estrogens on levels of tenofovir diphosphate (the active form of tenofovir) in genital tissues have been conflicting. Because of concern for possible effects of estrogen on tenofovir diphosphate levels, oral PrEP should utilize daily dosing and not on-demand (2-1-1) dosing. There are no published data on the impact of estrogens on cabotegravir genital tissue levels, but a study of oral cabotegravir with estradiol-containing contraception found that steady state pharmacokinetic levels of cabotegravir were as expected, suggesting there is likely no significant interaction, though more data would be useful.

Persons in Periconception, Antepartum, and Postpartum Periods: Individuals with a uterus are at increased risk of HIV acquisition during the periconception period due to more frequent condomless sex and biological factors, such as alterations in adaptive immunity, increased genital tract inflammation, and changes to the vaginal microbiome. 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. The Perinatal HIV Clinical Guidelines now strongly recommend offering once-daily tenofovir DF-emtricitabine as HIV PrEP to pregnant people at risk for HIV acquisition, regardless of whether they are trying to conceive, are pregnant, or are breastfeeding. Pregnant people 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 prevention strategies should be used in the interim. The Perinatal HIV Clinical Guidelines and Perinatal HIV Clinical Guidelines recommend that if a person becomes pregnant while taking daily oral tenofovir DF-emtricitabine and the risk of HIV exposure is ongoing, they can continue it. No data exist for the use of on-demand tenofovir DF-emtricitabine PrEP for individuals with vaginal exposure to HIV. Tenofovir alafenamide-emtricitabine is not indicted for PrEP in women. Although cabotegravir is indicated for use in women to prevent HIV, there are no data on cabotegravir in pregnancy or in breastfeeding.
Baseline Laboratory Evaluation, Immunizations, and Counseling

Baseline Laboratory Studies

The 2021 CDC PrEP Clinical Practice Guideline recommends performing a risk assessment and baseline laboratory evaluation prior to prescribing HIV PrEP. In order to qualify for HIV PrEP, an individual should have substantial, ongoing risk for HIV and a baseline laboratory evaluation that includes the following:

- **HIV Testing**: For persons starting oral HIV PrEP, baseline HIV testing, ideally with a laboratory HIV-1/2 antigen-antibody immunoassay, with reflex HIV-1/2 antibody differentiation assay confirmation, should be performed within 1 week of starting. Alternatively, a point-of-care fingerstick blood test can be performed for the initial HIV screening test. Note that oral point-of-care HIV tests are not recommended for HIV testing prior to starting HIV PrEP due to the low sensitivity of these tests for diagnosing recent HIV infection. For persons starting cabotegravir, HIV testing should also include an HIV RNA test, including prior to starting oral cabotegravir (if used as a lead in) and prior to the first injection. 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) or a single agent (cabotegravir) in a person with HIV infection would provide inadequate treatment and likely result in the development of significant HIV drug resistance.

- **Renal Function**: For persons planning to receive either tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, 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 HIV PrEP. Similarly, persons with estimated creatinine clearance less than 30 mL/min should not receive tenofovir alafenamide-emtricitabine for HIV PrEP. Baseline laboratory studies to evaluate renal function are not required for persons starting on injectable cabotegravir (with or without an oral lead in).

- **Sexually Transmitted Infections**: Baseline testing for sexually transmitted infections should include testing for gonorrhea, chlamydia, and syphilis. Testing for syphilis requires a blood draw. Testing for gonorrhea and chlamydia should utilize nucleic acid testing (NAT) and samples should be obtained from anatomic sites of sexual exposure.

- **Lipid Panel**: Persons who receive tenofovir alafenamide-emtricitabine should have a baseline lipid panel as tenofovir alafenamide-emtricitabine can cause alterations in serum lipids, including elevated triglyceride levels. When tenofovir alafenamide-emtricitabine and tenofovir DF-emtricitabine are compared, lipid parameters are higher with the tenofovir alafenamide option, though whether this is clinically significant remains controversial.

- **Hepatitis B**: For all persons 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 who have 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. Furthermore, as of 2023, the CDC recommends that all adults in the United States undergo screening for hepatitis B infection at least one time.

- **Hepatitis C**: For persons who are starting HIV PrEP, baseline screening for hepatitis C virus (HCV) infection should be performed for all MSM, transgender women who have sex with men, and persons who inject drugs. Testing for HCV infection should consist of an initial HCV antibody test, followed by HCV RNA testing for all positive HCV antibody tests. For persons who have never had testing for HCV, a one-time HCV testing is recommended for all adults in the United States who are 18 years of age and older.
**Immunizations**

The evaluation and management of persons receiving HIV PrEP also provides an opportunity to counsel and administer 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.[42] In addition, hepatitis A immunization is recommended for certain populations that may overlap with persons seeking PrEP, including MSM and persons who inject drugs.[43] 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.[42, 44] Individuals with elevated risk for HIV acquisition might also have an increased risk of acquiring mpox virus and thus would also benefit from vaccination with the mpox vaccine.[45] Screening for potential HIV PrEP use is also an opportunity to review whether a person has received routine, recommended vaccinations and offer immunizations if they have not received recommended immunizations.

**Behavioral Risk Reduction Counseling**

Because high medication adherence is critical to HIV PrEP efficacy, but is often not achieved, individuals at risk of acquiring HIV 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.[10] In addition, it is important to counsel persons who take HIV PrEP that HIV PrEP medications do not prevent acquisition of bacterial sexually transmitted infections or infections, such as hepatitis C virus, that can be acquired from sharing injecting needles or other injecting equipment.
Major HIV PrEP Studies

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

Men Who have Sex with Men and Transgender Women Who have Sex with Men

- **DISCOVER**: This phase 3, randomized, double-blind trial compared the safety and efficacy of daily oral tenofovir alafenamide-emtricitabine with daily oral tenofovir DF-emtricitabine for HIV PrEP in adult MSM and adult transgender women who have sex with men.[25] The study enrolled a total of 5,387 persons in the United States and Canada, of whom 1% were transgender women.[25] 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.[25] Participants receiving tenofovir alafenamide-emtricitabine, when compared with those receiving tenofovir DF-emtricitabine, had favorable bone mineral density measurements and biomarkers of renal safety, but experienced more weight gain (about 1.2 kg difference).[25]

- **HPTN 083**: The 083 study was a randomized, double-blind, double-dummy, noninferiority trial to compare long-acting injectable cabotegravir with daily oral tenofovir DF-emtricitabine for the prevention of HIV infection in cisgender MSM and transgender women who have sex with men.[16] The cabotegravir regimen consisted of a 5-week lead-in with oral cabotegravir (30 mg daily), followed by 2 doses of intramuscular cabotegravir (600 mg) 4 weeks apart, followed by injectable cabotegravir every 8 weeks.[16] There were 39 new HIV infections (incidence 1.22 per 100 person-years) in the tenofovir DF-emtricitabine group and 13 infections (incidence 0.41 per 100 person-years) in the cabotegravir arm. Long-acting injectable cabotegravir was superior to tenofovir DF-emtricitabine for the prevention of HIV in MSM and transgender women; superior efficacy of long-acting cabotegravir was driven largely by imperfect adherence to oral tenofovir DF-emtricitabine in that arm of the trial.[16]

- **IPrEx**: The Iniciativa Profilaxis Pre-Exposición (iPrEx) study was a phase 3, randomized, double-blind, placebo-controlled trial conducted in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States that enrolled 2,499 HIV-seronegative adults, including 2,470 MSM and 29 transgender women who have sex with men.[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 assessment, and dispensing of pills and condoms. This study documented 44% fewer new HIV infections among those who received daily tenofovir DF-emtricitabine for PrEP when compared to those who received placebo.[18] The reduction in new HIV infections was much higher (92%) when limiting the analysis to participants with detectable levels of study drug (indicating adherence to the medication).[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 (referred to as intermittent, on demand, or 2-1-1 dosing) for the prevention of HIV among 400 sexually active MSM and transgender women who have sex with men.[20] Participants were evaluated at weeks 4 and 8, and then every 8 weeks thereafter. In addition, 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 condomless anal sex with men in the previous 90 days.[19] 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%.[19] The estimated number needed to treat to prevent one case of new HIV acquisition was only 13.[19]

**Cisgender 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 HIV acquisition.[21] The partners with HIV had a median CD4 count of 495 cells/mm³ and were not receiving antiretroviral therapy (because they were not eligible per local treatment guidelines that existed at the time the study was conducted).[21] The trial was stopped after an interim analysis 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.[21] 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.[22] In this study, daily oral use of tenofovir DF-emtricitabine resulted in a 62% reduction in HIV acquisition when compared with placebo.[22] Adherence by pill count was 84% in both medication groups.

**Cisgender Women**

- **HPTN 084 (LIFE Study)**: The 084 study was a phase Ib/3, randomized, double-blind trial to compare long-acting injectable cabotegravir with daily oral tenofovir DF-emtricitabine for the prevention of HIV infection in cisgender women at risk for acquiring HIV.[17] The cabotegravir regimen consisted of a 5-week lead in with oral cabotegravir (30 mg daily), followed by 2 doses of intramuscular cabotegravir (600 mg) 4 weeks apart, followed by injectable cabotegravir every 8 weeks.[17] There were 34 new HIV infections (incidence 1.79 per 100 person years) in the tenofovir DF-emtricitabine group and 4 infections (incidence 0.21 per 100 person years) in the cabotegravir arm. Long-acting injectable cabotegravir demonstrated superior efficacy, as compared with tenofovir DF-emtricitabine for the prevention of HIV in cisgender women.[17]

- **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 cisgender, heterosexual women in South Africa, Kenya, and Tanzania.[46] Participants were seen at monthly follow-up visits, and the study drug was discontinued among women who became pregnant during the trial.[46] 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.[46] Adherence was low in this trial, with detectable plasma drug levels in less than 50% of the women assigned to tenofovir DF-emtricitabine.[46]

- **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, cisgender 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.[47] 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.[47] Use of the dapivirine ring reduced overall HIV incidence by 27%, and higher adherence rates correlated with greater HIV protection.[47] 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).[47]

- **Ring**: The Ring study was a phase 3, double-blind, placebo-controlled trial in which 1,959 sexually active, cisgender 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.[48] 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.[48] 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.[48] The HIV protection differed with age; the efficacy of HIV protection was 37% among women older than 21 years of age (a subgroup with higher rates of adherence) compared with 15% among women younger than age 21 (a subgroup with lower markers of adherence).[48]

- **VOICE**: The Vaginal and Oral Interventions to Control the Epidemic (VOICE) study was a randomized, placebo-controlled trial that enrolled reproductive age, cisgender women and randomized them to one of three HIV preventative medications (oral tenofovir DF-emtricitabine daily, oral tenofovir DF daily, or a 1% tenofovir vaginal gel) versus placebo.[49] A total 5,029 participants were enrolled at 15 sites in South Africa, Uganda, and Zimbabwe.[49] None of the study arms were found to be effective at reducing the likelihood of HIV transmission as compared to placebo, but adherence to the study drugs was documented to be low.[49] Based on random samples, tenofovir was detected in blood in 30% or fewer participants in all study arms, which likely explains why the HIV PrEP options did not reduce HIV incidence compared to placebo.[49] Individuals who were older than 25 years of age, married, and multiparous were more likely to have detectable plasma tenofovir levels (indicating adherence), suggesting that participants who were younger and unmarried were less likely to adhere to the medications.[49] Participants reported that they were unsure of the efficacy and safety of the medications and feared that they would be mistakenly identified as having HIV if the pills were discovered.[50] Stigma about HIV and HIV medications proved to be a major barrier to adherence in the trial.

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**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.[23] All participants also received access to addiction support services, methadone programs, bleach for cleaning needles, condoms, and primary care medical services.[23] 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.[23]
Time to Achieve Protection after Initiating HIV PrEP

After initiating oral HIV PrEP with tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, these medications must reach the body tissues and then undergo phosphorylation to function as inhibitors of HIV replication. Available data in humans suggest that with oral ingestion of tenofovir DF, the maximal concentrations of tenofovir diphosphate (the active form of tenofovir) are obtained in peripheral blood mononuclear cells in about 7 days, rectal tissues by about 7 days, and cervicovaginal tissues at about 20 days.[51,52,53] Similar data for tenofovir alafenamide or cabotegravir are not known. Furthermore, there is no consensus as to the required time to reach protective levels (as opposed to maximum levels). The 2021 CDC 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.[54] The 2022 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, and these guidelines comment that for cisgender men starting with a double-dose of tenofovir DF-emtricitabine on the first day likely leads to protective levels by 24 hours (extrapolating data from the 2-1-1 studies).[11] It should be noted, however, that data for time to protective levels are limited, so many experts continue to use 7 days as the recommendation time to protection for cisgender men. Accordingly, there are no official recommendations regarding how long it would take to achieve protection against HIV acquisition after initiating injectable cabotegravir for HIV PrEP. The 2022 IAS-USA HIV Treatment and Prevention Recommendations comment that onset of HIV protection is likely to be approximately 7 days after the first cabotegravir injection, but further research is needed to confirm this estimate.[11]
Impact of Adherence on Efficacy of HIV PrEP

In the HIV PrEP trials completed to date, adherence to HIV PrEP has been the single most important factor that impacts efficacy.[4,55,56] The correlation of adherence with oral HIV PrEP efficacy has been strongest when adherence estimates are based on detection of tenofovir in blood samples (Figure 8).[57] For example, 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 acquired HIV during the study (Figure 9).[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.[21] Similarly, poor adherence has correlated with lack of HIV PrEP benefit as shown in the FEM-PrEP and VOICE trials.[46,55] The effectiveness of HIV PrEP outside of clinical trials has been found to be lower than in trials, especially for younger individuals and for persons with added adherence challenges due to certain social determinants of health.[58] Because of the extreme importance of good adherence to achieve high HIV PrEP efficacy, regular adherence counseling is recommended for all persons taking HIV PrEP (Table 1).[9]
Laboratory Monitoring on HIV PrEP

All individuals taking HIV PrEP should have laboratory monitoring as part of their routine follow-up evaluations, but the specific follow-up differs depending on whether the person is taking tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine, or cabotegravir.[9] These follow-up evaluations should take place every 3 months for persons taking oral PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine) and every 2 months for those taking injectable cabotegravir. The 2021 CDC PrEP Clinical Practice Guideline recommends the following regarding laboratory monitoring for persons taking HIV PrEP:[9]

- **HIV Testing**: Repeat HIV testing and evaluation for signs and symptoms of acute HIV infection should be performed at least every 3 months for those persons taking oral PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide) and every 2 months for those taking long-acting injectable cabotegravir; in addition, persons receiving cabotegravir should have HIV testing performed 1 month after the first injection. The recommended HIV testing should include both an HIV-1/2 antigen-antibody test and an HIV-1 RNA assay (qualitative or quantitative). The rationale for including HIV-1 RNA in routine testing is that recent data have shown a less than optimal performance with standard HIV-1/2 antigen-antibody testing in persons who acquire HIV while taking antiretroviral medications. That said, if cost or coverage issues prevent the ability to order an HIV RNA test and a person has an indication for HIV PrEP, most experts would prescribe HIV PrEP and perform the best available test for HIV screening. In other words, the inability to access regular HIV RNA testing should not preclude HIV PrEP if a person has a strong indication.

- **Monitoring Renal Function**: Monitoring for renal function should be performed for all persons receiving oral PrEP. Renal function should be assessed every 6 months if the individual is 50 years of age and older, or they have a baseline estimated creatinine clearance of less than 90 mL/min. Persons who are younger than 50 years of age and who have a baseline estimated creatinine clearance of at least 90 mL/min should have renal monitoring every 12 months. Monitoring of renal function is not necessary for persons receiving injectable cabotegravir.

- **Lipid Panel and Weight Monitoring**: Persons receiving tenofovir-alafenamide should have monitoring every 12 months for cholesterol levels, triglyceride levels, and weight.

- **Hepatitis C Serology**: Repeat hepatitis C serologic testing should be performed every 12 months for MSM, transgender women who have sex with men, and persons who inject drugs.

- **Sexually Transmitted Infections (STIs)**: For MSM and transgender women who have sex with men, screening for bacterial STIs (chlamydia, gonorrhea, and syphilis) should occur at least every 3 months if taking oral HIV PrEP and at least every 4 months if receiving injectable cabotegravir. For heterosexually active cisgender women and cisgender men who are taking oral HIV PrEP or receiving injectable cabotegravir, screening for syphilis and gonorrhea should occur every 6 months and screening for chlamydia every 12 months. Screening for chlamydia and gonorrhea should use NAT and include all appropriate body sites based on reported sexual activity.

- **Pregnancy Testing**: For individuals who might become pregnant while taking HIV PrEP, pregnancy testing should be performed at least every 3 months. If a person becomes pregnant (or is breastfeeding) while taking PrEP, the clinician prescribing HIV PrEP should have a discussion with the person and their prenatal medical provider about the risks and benefits of continuing HIV PrEP during pregnancy.
Acquisition of HIV in the Setting of HIV PrEP

If HIV infection is documented at the baseline evaluation or via a follow-up evaluation, then a number of subsequent steps should occur.[9]

- **Laboratory Studies**: In persons newly diagnosed with HIV, laboratory studies should be ordered that include a quantitative 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, which typically means higher than 200 to 500 copies/mL). If an individual is taking or has taken long-acting injectable cabotegravir for HIV PrEP and acquires HIV, the HIV genotypic resistance testing should include testing integrase resistance assay (this integrase genotype typically requires a separate order from the standard genotype).[59]

- **Initiating Antiretroviral Treatment Regimen**: Once a diagnosis of HIV is made, it is important to start a fully suppressive HIV regimen (if the diagnosis is at the baseline evaluation) or convert the HIV PrEP regimen to a full antiretroviral treatment regimen if the person is receiving or recently received HIV PrEP.[10] If needed, the antiretroviral regimen can be modified when the results from the genotype become available.[60] In general, if a person acquires HIV and has current or recent exposure to oral PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine), the change to antiretroviral treatment should involve addition of a potent integrase inhibitor (by adding dolutegravir to the tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine or by prescribing bictegravir-tenofovir alafenamide-emtricitabine).[60] On the other hand, if a person acquires HIV and has had exposure to injectable cabotegravir, due to the risk of integrase resistance, the initial antiretroviral therapy regimen should be boosted darunavir plus two NRTIs (tenofovir DF or tenofovir alafenamide) plus (emtricitabine or lamivudine); the boosted darunavir can be switched to an integrase inhibitor if the integrase genotype confirms no resistance.[60]

- **Provide or Link to HIV Treatment Services**: 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 treatment expertise.

- **Counseling and Partner Notification**: The person newly diagnosed with HIV should receive counseling about their HIV status and steps they should take to prevent HIV transmission to others. Partner notification should occur with all persons newly diagnosed with HIV.
HIV PrEP and Development of HIV Drug Resistance

HIV Drug Resistance in Persons Taking HIV PrEP

Although development of drug resistance is a concern for an individual who acquires HIV while taking tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine, or injectable cabotegravir, large HIV PrEP trials have reported low rates of developing HIV resistance when taking HIV PrEP. In the iPrEx study, only 2 of the 48 persons taking tenofovir DF-emtricitabine who acquired HIV showed resistance mutations, and these minor variant mutations (e.g., M184I) were detected only with deep sequencing. In the Partners PrEP study, 5 of 63 seroconverters (7.9%) in the active PrEP arms of the study developed HIV drug resistance, and resistance was more common in persons assigned to the tenofovir DF-emtricitabine arm compared with the tenofovir DF only arm. In the cabotegravir HPTN 083 study, integrase strand transfer inhibitor resistance was documented in 4 of 9 breakthrough infections among persons in the cabotegravir arm; reverse-transcriptase inhibitor mutations (K65R, M184V, M184I) were observed in 4 persons who had breakthrough HIV infections while taking tenofovir DF-emtricitabine. Taken together, available data suggest that PrEP-related HIV drug resistance will occur at a low rate as long as HIV infection is ruled out prior to starting HIV PrEP and persons taking HIV PrEP have regular HIV testing, with those who newly acquire HIV immediately modifying the HIV PrEP regimen to a fully suppressive antiretroviral regimen.

Evaluation for Suspected HIV Drug Resistance

An HIV RNA level and an HIV genotype resistance assay should be ordered promptly for any person taking HIV PrEP who is diagnosed with HIV. In some instances, however, individuals who acquire HIV while taking PrEP may have detectable HIV RNA but at a level below the range for reliable performance of HIV genotyping. This scenario occurs because HIV PrEP medication is partially suppressing viral replication. In this setting, the role of HIV DNA genotyping (also known as a proviral genotype), which can be performed with very low or undetectable HIV RNA levels, has not been clearly defined. If a person acquires HIV while taking oral PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine) or with recent exposure to oral HIV PrEP, the baseline genotype upon diagnosis of HIV can be a standard genotype that assesses for mutations in the reverse transcriptase and protease genes (the primary purpose is to assess for mutations that would compromise the NRTI backbone of a treatment regimen). If, however, a person acquires HIV and has previously received injectable cabotegravir, regardless of the time since last injection or since drug discontinuation (because the drug has a very long half-life), the baseline genotype should also include a check for resistance-associated mutations in the integrase gene (to assess for mutations that would affect the anti-HIV activity of the integrase inhibitor mutations). Depending on the lab, this may require a separate order.

Monitoring for HIV Infection to Prevent Resistance

Baseline HIV testing prior to starting HIV PrEP is essential to make sure an individual with HIV does not start taking a regimen that would be inadequate for HIV and that would lead to rapid development of drug resistance. For persons taking HIV PrEP, regular HIV testing is extremely important to minimize the duration of exposure to medications if they acquire HIV while taking HIV PrEP. Furthermore, to minimize the risk of developing resistance among persons taking oral HIV PrEP, the 2021 CDC PrEP Clinical Practice Guideline recommends prescribing no more than 90 days of medication at a time and repeating HIV testing every 3 months. For MSM receiving on-demand (2-1-1) HIV PrEP with tenofovir DF-emtricitabine, a maximum of 30 pills should be provided before repeat HIV testing is performed, which would provide adequate medication for 7 exposure events. Individuals taking injectable cabotegravir should have HIV testing at the time of the initial 1-month injection visit and then every 2 months thereafter (following the same schedule as the injections). The recommended HIV testing for persons receiving oral PrEP or injectable cabotegravir should include both an HIV-1/2 antigen-antibody assay and HIV-1 RNA testing. Any person who develops symptoms consistent with acute HIV should also have HIV testing, including an HIV RNA assay.
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 (sometimes referred to as “start-up syndrome”).[5,54] 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 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.[63,64,65] 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. Therefore, monitoring of renal function is recommended in all persons taking tenofovir DF-emtricitabine for HIV PrEP.[54] 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.[66,67,68,69] 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.[70] Although tenofovir DF could potentially impact bone density, routine baseline (or follow-up) bone density scanning is not considered necessary. For a person who has documented osteoporosis or osteopenia or risk factors for such, some experts would opt for alternate HIV PrEP options if possible.

Adverse Effects with Tenofovir alafenamide-Emtricitabine

In most persons, tenofovir alafenamide-emtricitabine is well tolerated and safe, with better bone and renal safety outcomes than tenofovir DF-emtricitabine.[25] Non-specific “start-up syndrome” symptoms may occur, for some individuals, similar to symptoms that may occur with tenofovir DF-emtricitabine. Weight gain, increases in cholesterol, and increases in triglyceride levels have been associated with tenofovir alafenamide-emtricitabine, though the mechanism and long-term consequences are not clear.[9,25].

Adverse Effects with Long-Acting Injectable Cabotegravir

Among persons receiving injectable cabotegravir, the most common adverse effect is injection site reactions, which resulted in the discontinuation of cabotegravir in only about 2% of persons receiving this medication.[16] In the cabotegravir HPTN 083 study, among persons who experienced an injection site reaction, the most common symptoms were pain (61%) and tenderness (24%).[16] Injection site reactions typically begin about 1 day after the injection and last about 3 days.[16] Most injection site reactions are mild, self-limited, and do not lead to discontinuation of the medication. Hot or cold packs and as-needed oral analgesics (anti-inflammatory medications and acetaminophen) can help to alleviate symptoms.
Changes in Sexual Practices Among Persons Receiving PrEP

Critics of HIV 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”. Part of this concern was fueled by two meta-analyses that suggested an increased rate of bacterial sexually transmitted infections for MSM taking HIV PrEP, as compared to MSM not taking HIV PrEP. In contrast, a systematic review that did not find conclusive evidence that taking HIV PrEP leads to an increase in risky sexual activities. The evidence in HIV PrEP clinical trials for risk compensation has been mixed, as summarized by key findings from the following HIV PrEP trials.

- **iPrEx**: 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 10).

- **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. 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.

- **Bangkok Tenofovir**: In the PrEP trial of persons who inject drugs in Thailand, rates of injecting drugs and sharing needles decreased at follow-up.

- **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.

- **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.

- **PROUD**: In this trial that enrolled cisgender MSM and randomized them to immediate versus deferred tenofovir DF-emtricitabine daily HIV PrEP, there was no difference in incidence of sexually transmitted infections between the two groups, even though some participants reported an increase in condomless sex.

At a population level, the impact of risk compensation with HIV PrEP remains unclear. Nevertheless, most experts believe the HIV prevention value of HIV PrEP outweighs any potential change in sexual practices that may occur while persons are receiving HIV PrEP. Individuals prescribed PrEP should always be counseled about other methods for risk reduction, counseled that the medication does not prevent bacterial STIs, and should undergo regular screening for bacterial STIs. Further, dissemination of PrEP can increase the rates of screening, detection, and treatment for STIs, which can be beneficial.
**Discontinuing PrEP**

There are a number of factors that may lead an individual to discontinue HIV PrEP, including a decline in HIV risk activity, medication-related side effects, or a positive HIV test. In general, HIV PrEP is indicated during periods of substantial risk of acquiring HIV, which may last for months or even years, but it should not typically be viewed as a life-long prevention strategy.\[5\] Several key factors should be taken into consideration at the time of discontinuing PrEP:\[9\]

- Upon discontinuation of HIV PrEP, 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.
- If an individual has chronic HBV infection and discontinues taking HIV PrEP with either tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, several months of monitoring for a possible HBV flare should occur, or consideration given for the treatment of chronic HBV, if indicated.
- For an individual planning to discontinue oral HIV PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine), the protection from HIV infection will wane over approximately 7 days after stopping the medication.
- Special consideration needs to be given when injectable cabotegravir is discontinued, since levels of the medication may remain in tissues for a year or longer (up to 4 years in some individuals).\[79\] If a person discontinues injectable cabotegravir but has an ongoing risk for HIV acquisition, oral HIV PrEP should be recommended as a high priority during the cabotegravir “tail period”, which can last 1 year or longer. In this setting, the oral HIV PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine) should be prescribed within 2 months of the last cabotegravir dose. In addition, all persons stopping cabotegravir should have quarterly follow-up visits that include HIV testing for at least 12 months after the last injection of cabotegravir.
- If the individual discontinues HIV PrEP for any reason other than acquiring HIV, they should continue to have HIV testing performed, linkage to HIV prevention support services, and continued risk-reduction counseling.
Transitioning from Nonoccupational PEP to PrEP

Indications for Transition from Nonoccupational PEP to PrEP

All persons who receive one or more courses of nonoccupational postexposure prophylaxis (PEP) and have ongoing or anticipated near-future risk for acquiring HIV should be considered for HIV PrEP. For persons with repeated exposures to HIV, the use of HIV PrEP is preferable to repeated courses of nonoccupational PEP.[9] At the initial visit for persons undergoing evaluation for nonoccupational PEP, the discussion should include information regarding potential transition to HIV PrEP after completing the 28-day course of nonoccupational PEP.

Timing of the Transition from Nonoccupational PEP to PrEP

For persons receiving nonoccupational PEP who are candidates to receive HIV PrEP, the transition from nonoccupational PEP to HIV PrEP should occur without any gap in protection for HIV infection (i.e. the transition should be immediate from completion of 28 days of PEP to initiation of PrEP on the subsequent day).[9,10,80] The major concern with immediate transition to HIV PrEP is that an individual could have acquired HIV from the exposure that warranted receipt of nonoccupational PEP. If this occurred, the potential for development of HIV resistance would be significant because the individual would be transitioning from nonoccupational PEP (a three-drug regimen) to PrEP (a 2-drug oral regimen or a 1-drug injectable cabotegravir regimen). This risk, however, appears to be very low, especially if adherence is good with occupational PEP and if baseline HIV testing is performed prior to the actual transition.

Evaluation when Transitioning from Nonoccupational PEP to PrEP

The following clinical and laboratory evaluation is recommended when transitioning an individual immediately from nonoccupational PEP to PrEP.[9,10] This transition requires some logistical considerations to ensure the individual begins HIV PrEP immediately upon completing the 28-day nonoccupational PEP regimen.[9,10]

- For persons who are candidates for transition from nonoccupational PEP to PrEP, a follow-up visit will be needed at the completion of the 28-day nonoccupational PEP regimen (or several days prior to completing the regimen). To ensure no gap in HIV protection occurs, it is important the visit does not take place on a date after completion of the 28-day course of nonoccupational PEP.
- At this follow-up visit, the individual should have an assessment for any signs or symptoms that would suggest acute HIV. If an individual is presenting with an illness consistent with acute HIV, then HIV PrEP should be deferred while evaluation of acute HIV is undertaken and this evaluation should include HIV RNA testing.
- Repeat HIV testing should be performed at this visit, ideally with a laboratory-based HIV-1/2 antigen-antibody immunoassay and an HIV RNA-1 assay. These assays typically require 1-3 days before results are available, which practically means they should be ordered several days prior to the end of the 28-day nonoccupational PEP course or the person can transition to PrEP at the 28-day visit while the results are pending, with the plan to immediately convert the PrEP to HIV treatment if the HIV testing reveals HIV infection.
- At this visit, individuals transitioning to HIV PrEP should receive counseling about HIV PrEP, and baseline laboratory studies that are indicated should be obtained. The medication regimen can transition from the 3-drug nonoccupational PEP to any of the three HIV PrEP regimens (tenofovir DF-emtricitabine, tenofovir alafenamide-emtricitabine, or long-acting injectable cabotegravir), as long as they are indicated for the individual.
- If HIV testing at any point prior to starting PrEP (or while on PrEP) confirms HIV infection, the individual will need prompt evaluation for the management of newly acquired HIV.
Disparities in HIV PrEP Use

Despite the overwhelming evidence favoring PrEP use for HIV prevention, there are substantial data demonstrating low rates of HIV PrEP uptake among persons who could benefit from taking HIV PrEP in certain demographic groups, particularly (1) Black and Hispanic men who have sex with men and (2) cisgender women.[13,81,82,83,84,85,86]

- **HIV PrEP Uptake by Gender:** Recent surveillance data from the CDC for 2021 indicate that among persons at risk for acquiring HIV, 34% of cisgender men who could benefit from HIV PrEP were prescribed HIV PrEP compared to 12% among cisgender women.[14] Moreover, the recent DISCOVER PrEP trial that evaluated tenofovir alafenamide-emtricitabine for PrEP excluded cisgender women—further contributing to the gender disparities for the use of PrEP in the United States.[25] 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.[87] 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.[87] A retrospective analysis following 13,906 insured persons who were prescribed PrEP in a large United States healthcare system found women, when compared with men, were less likely to receive and initiate PrEP and more likely to discontinue PrEP once it was started.[88]

- **HIV PrEP Update by Race:** Among persons with an HIV PrEP indication, the highest percentage of persons prescribed HIV PrEP was in White people (78%), which was a markedly higher percentage than in Hispanic people (21%) and in Black people (11%).[14] The reasons for these differences are complicated and likely involve many factors, including stigma, access to care, and other health disparities. 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 can help to provide HIV PrEP equally to all populations.

- **HIV PrEP Update by Age:** Among persons in different age groups, persons 16-24 years of age had the lowest percentage of persons with an HIV PrEP indication who had HIV PrEP prescribed for them.[14]
Future HIV PrEP Medications

Further studies are underway to investigate different delivery systems for HIV PrEP as well as different active antiretroviral agents. Some of these novel HIV PrEP strategies that are not FDA-approved in the United States for HIV PrEP include oral or injectable lenacapavir (a capsid inhibitor) and oral or injectable islatravir (a nucleoside reverse transcriptase translocation inhibitor).[89,90] Novel delivery systems, including microarray patches, vaginal films, implants (including ultra long-acting, refillable implants), and others, are also in development.[91] An ongoing study evaluating the efficacy of lenacapavir as HIVPrEP is comparing it to oral tenofovir alafenamide-emtricitabine for cisgender women; thus, the trial will give important efficacy and safety data of both a long-acting injectable agent (lenacapavir, dosed as a subcutaneous injection every 6 months) and tenofovir alafenamide-emtricitabine for individuals with vaginal exposure as the risk factor for HIV. There has been strong development and global interest in the dapivirine vaginal ring, but the dapivirine application for FDA approval in the United States has been withdrawn, but other vaginal rings are in development.[48,92] The future for HIV PrEP medications is likely to include a greater array of medication and delivery system options.
Summary Points

- Antiretroviral HIV 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 oral tenofovir DF-emtricitabine, oral tenofovir alafenamide-emtricitabine, and long-acting injectable cabotegravir. Note that tenofovir alafenamide-emtricitabine is not indicated for cisgender women or other individuals whose risk factor for HIV acquisition is receptive vaginal sex.
- A risk assessment and baseline laboratory evaluation is required prior to prescribing HIV PrEP, including documentation that the person to receive HIV PrEP has a negative baseline HIV test.
- Monitoring for persons receiving oral HIV PrEP should include HIV testing (HIV-1/2 antigen-antibody testing plus an HIV-1 RNA assay) every 3 months for those on oral medications and every 2 months with long-acting injectable cabotegravir. Regular screening for STIs should occur in all persons receiving HIV PrEP.
- For persons receiving oral HIV PrEP with tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine, renal monitoring should occur every 6 or 12 months depending on the individual’s age and baseline estimated CrCl.
- Adherence to HIV PrEP medications has been the single most important factor that impacts efficacy in the clinical trials of PrEP.
- The risk of developing HIV drug resistance associated with HIV 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 from 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


26. 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]


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Figures

Figure 1 Estimated HIV Incidence in United States, 2017-2021

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

Figure 2 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface (Image Series)

**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
Figure 2 (Image Series) - Sexual Transmission of HIV at Genital Mucosal Surface
Image 2D: 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
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 HIV 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.

Illustration by David H. Spach, MD
Figure 4 Daily Oral HIV 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: David H. Spach, MD
Figure 5 On-Demand (2-1-1) Oral HIV Preexposure Prophylaxis

The only recommended medication for on-demand (2-1-1) dosing for HIV preexposure prophylaxis is oral tenofovir DF-emtricitabine. This option is considered off-label and has only been studied for cisgender MSM. It may be an appropriate option if condomless sex occurs frequently and the individual can anticipate sex and adhere to the on-demand dosing schedule. For this example of a single sexual encounter, the individual take a loading dose of 2 pills 2-24 hours before the sexual encounter and then take one pill 24 hours after the first dose and one pill 48 hours after the first dose.

Illustration: David H. Spach, MD
**Figure 6 Long-Acting Injectable HIV Preexposure Prophylaxis**

Cabotegravir is the only medication that is FDA-approved as a long-acting injectable for HIV PrEP. It is administered as a gluteal intramuscular injection every 2 months, after two initial injections that are 1 month apart.

Illustration: David H. Spach, MD
Figure 7 HIV PrEP Coverage, United States, 2017-2022


*Calculated as number of persons prescribed HIV PrEP divided by estimated number of persons with indications for HIV PrEP
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 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 10 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.

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<thead>
<tr>
<th>Establish trust and bidirectional communication</th>
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<tr>
<td>• Medication dosage and schedule</td>
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<tr>
<td>• Management of common side effects</td>
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<tr>
<td>• Relationship of adherence to the efficacy of PrEP</td>
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<tr>
<td>• Signs and symptoms of acute HIV infection and recommended actions</td>
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<th>Support adherence</th>
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<tr>
<td>• Tailor daily dose to patient’s daily routine</td>
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<td>• Identify reminders and devices to minimize forgetting doses</td>
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<tr>
<td>• Identify and address barriers to adherence</td>
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<tr>
<td>• Reinforce benefit relative to uncommon harms</td>
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<th>Monitor behavioral adherence in a nonjudgmental manner</th>
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<td>• Normalize occasional missed doses, while ensuring patient understands importance of daily dosing for optimal protection</td>
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<td>• Reinforce success</td>
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<td>• Identify factors interfering with adherence and plan with patient to address them</td>
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<tr>
<td>• Assess side effects and plan how to manage them</td>
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