HIV Preexposure Prophylaxis (PrEP)

This is a PDF version of the following document:
Module 5: Prevention of HIV
Lesson 5: HIV Preexposure Prophylaxis (PrEP)

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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).[1,2] Furthermore, significant geographic and demographic differences exist for HIV infection rates within the United States HIV epidemic, with the bulk of new infections occurring among young men who have sex with men (MSM), with particularly high rates among Black and Hispanic men in the South.[1,3] 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.[4] An expanding number of HIV prevention methods are being implemented worldwide, and HIV preexposure prophylaxis (PrEP) is now accepted as an important prevention strategy.[4,5] The expanded use of HIV PrEP is a major component in the national initiative—Ending the HIV Epidemic: A Plan for the United States.[6]

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.[5,7,8] Most often, HIV PrEP is used to prevent sexual transmission of HIV, but it has also been used to prevent transmission of HIV associated with injection drug use. In the absence of HIV PrEP, sexual transmission of HIV can occur as HIV crosses the mucosal surfaces to infect susceptible cells. After taking daily oral HIV PrEP or receiving injections of cabotegravir or lenacapavir, cells susceptible to HIV achieve adequate intracellular concentrations of the antiretroviral medication(s) to block replication of HIV following an exposure. There are now three fundamental types of HIV PrEP that are used in the United States: (1) daily oral HIV PrEP with either oral tenofovir DF-emtricitabine or oral tenofovir alafenamide-emtricitabine, (2) on-demand (2-1-1) dosing using oral tenofovir DF-emtricitabine, and (3) long-acting injectable HIV PrEP (using intramuscular cabotegravir [cabotegravir-IM] or subcutaneous lenacapavir [lenacapavir-SQ]).[9] (Figure 2)

Guidelines for HIV 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.[9,10]
- **International Antiviral Society-USA (IAS-USA)**: In December 2022, the International Antiviral Society-USA Panel (IAS-USA) updated the Antiretroviral Drugs for Treatment and Prevention of HIV

Infection in Adults guidelines, which include recommendations for prescribing oral and injectable HIV PrEP.[11] The IAS-USA issued a brief update in 2025 that focused on use of lenacapavir-SQ for HIV PrEP.

- **United States Preventive Services Task Force (USPSTF)**: In August 2023, the United States Preventive Services Task Force (USPSTF) gave a Grade A recommendation for the use of HIV PrEP by clinicians to reduce HIV acquisition in persons at risk of acquiring HIV.[12,13]

Persons to Consider for HIV PrEP

In the United States, it is estimated that approximately 1.2 million persons have an HIV PrEP indication.[9,14] 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 HIV PrEP (Figure 3).[15,16] In addition, significant differences in access to and receipt of HIV PrEP persist based on socioeconomic and demographic factors, such as region of residence, sex, age, race, ethnicity, insurance status, residing in a state with expanded Medicaid or an HIV PrEP drug assistance program, as well as other factors.

Screening for HIV PrEP

Health care professionals should provide all sexually active adult and adolescent persons with information regarding HIV PrEP.[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, 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: oral tenofovir DF-emtricitabine, oral tenofovir alafenamide-emtricitabine, and long-acting injectable cabotegravir, and long-acting injectable lenacapavir.[17,18]

Tenofovir DF-emtricitabine (Oral)

- **Approved Indication for HIV PrEP**: In July 2012, the FDA approved tenofovir DF-emtricitabine for HIV PrEP.[19] Tenofovir DF-emtricitabine is indicated for HIV PrEP to reduce the risk of sexually-acquired HIV in adults and adolescents (weighing at least 35 kg). Individuals must have a negative HIV test prior to starting tenofovir DF-emtricitabine for HIV PrEP.
- **Formulation**: Tenofovir DF-emtricitabine is a two-drug, fixed-dose combination that contains 300 mg of tenofovir DF and 200 mg of emtricitabine. Oral tenofovir DF-emtricitabine can be taken with or without food.
- **Dosing**: The recommended dosing of tenofovir DF-emtricitabine when used for HIV PrEP is one tablet once daily. Alternative dosing, such as on-demand (2-1-1) dosing, is not included in the FDA indication but can be considered “off-label” for select MSM, per CDC guidelines.
- **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.
- **Key Studies**: 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,[20,21,22] men and women in heterosexual HIV-serodifferent couples (one person has HIV and the other does not),[23] heterosexual men and women recruited as individuals,[24] In addition, tenofovir DF alone was shown to be safe and effective as HIV PrEP for persons who inject drugs.[25]

Tenofovir alafenamide-emtricitabine (Oral)

- **Approved Indication for HIV PrEP**: Tenofovir alafenamide-emtricitabine is indicated for HIV PrEP in adults and adolescents (weighing at least 35 kg) who are at risk of acquiring HIV sexually, excluding women at risk from receptive vaginal sex.[26] Tenofovir alafenamide-emtricitabine is not indicated for receptive vaginal sex because its 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. Individuals must have a negative HIV test prior to starting tenofovir alafenamide-emtricitabine for HIV PrEP.
- **Formulation**: Tenofovir alafenamide-emtricitabine is a two-drug, fixed-dose combination that contains 25 mg of tenofovir alafenamide and 200 mg of emtricitabine. Oral tenofovir alafenamide-emtricitabine can be taken with or without food.
- **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.
- **Use in Persons with Renal Impairment**: For HIV PrEP, tenofovir alafenamide-emtricitabine is not recommended for persons who have an estimated creatinine clearance of less than 30 mL/min, unless they are on dialysis. For those on dialysis, tenofovir alafenamide-emtricitabine should be given after dialysis on the days when dialysis is performed.

Cabotegravir-IM (Long-Acting Injectable)

- **FDA-Approved Indication for HIV PrEP**: Long-acting injectable cabotegravir, administered as an intramuscular dose (cabotegravir-IM), is indicated as HIV PrEP for adults and adolescents (weighing at least 35 kg) who are at risk of sexual acquisition of HIV. Cabotegravir-IM has not been studied as a prevention measure for people who are at risk of acquiring HIV from injecting drugs.
- **Formulations**: Cabotegravir-IM 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, with or without food.

- **Dosing**: Cabotegravir-IM is administered 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 lead-in with oral 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-IM should be given on the last day of the oral lead-in (or within 3 days of completing the oral lead-in).
- **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. Hemodialysis is not expected to impact cabotegravir levels.

Lenacapavir-SQ (Long-Acting Injectable)

- **FDA-Approved Indication for HIV PrEP**: Long-acting injectable lenacapavir, administered as an subcutaneous dose (lenacapavir-SQ), is indicated for HIV PrEP to reduce the risk of sexually-acquired HIV-1 in adults and adolescents who weigh at least 35 kg (77 lbs). There are two lenacapavir-SQ medications available for commercial use—lenacapavir-SQ (*Yeztugo*) for HIV PrEP and lenacapavir-SQ (*Sunlenca*) for HIV treatment. Although these two lenacapavir-SQ medications contain the same recommended dose and dosing frequency, it is important to designate the correct brand, based on whether HIV PrEP is the indication or HIV treatment. In addition, there are two different oral brand preparations: oral lenacapavir (*Yeztugo*) for HIV PrEP and oral lenacapavir (*Sunlenca*) for HIV treatment.
- **Formulations**: Lenacapavir-SQ is available in 1.5 mL vials that contain 463.5 mg of lenacapavir. Lenacapavir is also available as a 300 mg tablet that can be taken with or without food.
- **Dosing**: Use of lenacapavir-SQ for HIV PrEP requires a 2-day initiation phase that uses both oral and injection doses. Day 1 of the initiation phase requires a 600 mg (2 x 300 mg tablets) dose of oral lenacapavir and a 927 mg (2 x 463.5 mg injections) of lenacapavir-SQ. Day 2 of the initiation phase requires a 600 mg (2 x 300 mg tablets) dose of oral lenacapavir. After the 2-day initiation phase, lenacapavir-SQ 927 mg (2 x 463.5 mg injections) is administered every 26 weeks.
- **Use in Persons with Renal Impairment**: There are no dosage adjustments of lenacapavir-SQ or oral lenacapavir in persons with mild, moderate, or severe renal insufficiency. There are insufficient data on the use of lenacapavir-SQ or oral lenacapavir in persons who have a creatinine clearance less than 15 mL/min). In addition, there are insufficient data on the use of lenacapavir-SQ or oral lenacapavir in persons receiving hemodialysis, but lenacapavir is highly protein bound and thus hemodialysis is not likely to significantly impact lenacapavir levels.

On-Demand (2-1-1) with tenofovir DF-emtricitabine

- **FDA-Approved Indication for HIV PrEP: D**osing with on-demand (2-1-1) HIV PrEP has not been approved
- **On-Demand (2-1-1) HIV PrEP**: The dosing with on-demand (2-1-1) HIV PrEP consists of taking oral tenofovir DF-emtricitabine before and after sex.[9] This approach to HIV PrEP was shown to be highly efficacious at preventing HIV in MSM in the large IPERGAY trial.[22] Although on-demand dosing is not FDA-approved for HIV PrEP in the United States, the 2021 CDC PrEP Clinical Practice Guideline recommends that on-demand (2-1-1) HIV PrEP with oral tenofovir DF-emtricitabine can be considered in selected adult MSM.[9] A person who starts on-demand HIV PrEP can change to daily oral HIV PrEP, or switch to an injectable medication (cabotegravir-IM or lenacapavir-SQ).
- **Dosing with On-Demand (2-1-1) HIV PrEP**: Dosing with on-demand HIV PrEP consists of taking 2 pills of tenofovir DF-emtricitabine 2 to 24 hours prior to sex, then 1 pill 24 hours after the initial 2 pills, and then 1 pill 48 hours after the initial 2 pills. If sexual activity continues on consecutive days, then 1 pill a day should continue to be taken for 48 hours after the last sexual event.[9] For MSM using demand 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 HIV PrEP should not be used for persons with chronic hepatitis B infection.

Additional Considerations

- **HIV PrEP for Persons who Inject Drugs**: Although no medication has 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 for HIV PrEP experienced a significant reduction in new HIV infections compared with persons taking placebo, with this benefit of PrEP occurring for both men and women.[25] Accordingly, persons who inject drugs should be considered for PrEP with daily tenofovir DF-emtricitabine to prevent the acquisition of HIV through injection drug use.[9,27] In addition, persons who inject drugs may also have a risk of sexual acquisition of HIV and, therefore, may have an indication for HIV PrEP separate from injection drug use.[9]
- **Women in Periconception, Antepartum, and Postpartum Periods**: Women are at increased risk of HIV acquisition during the periconception period due to multiple factors.[28,29,30] There are substantial data in women demonstrating the safety of tenofovir DF-emtricitabine for HIV PrEP and for treatment of HIV during the periconception, antepartum, and postpartum periods.[24,31,32] If HIV PrEP is indicated during pregnancy, the recommended regimen is daily oral tenofovir DF-emtricitabine.[33] In addition, if a woman becomes pregnant while taking daily oral tenofovir DF-emtricitabine for HIV PrEP, and the risk of HIV exposure is ongoing, she can continue this medication. Tenofovir alafenamide-emtricitabine is not recommended as HIV PrEP during pregnancy since it is not recommended for the prevention of vaginal acquisition of HIV. Although cabotegravir is indicated for use in women, it is not recommended during pregnancy or breastfeeding, due to inadequate data in this setting.

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.[9] 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.[9]

- **HIV Testing**: All persons starting HIV PrEP require baseline HIV testing and the testing should occur within 7 days prior to starting HIV PrEP. For persons starting oral HIV PrEP, baseline HIV testing, ideally with a laboratory blood-based HIV-1/2 antigen-antibody test. Alternatively, a point-of-care blood-based HIV antigen-antibody fingerstick blood test can be performed for the initial HIV screening test, with confirmation of negative results with a laboratory blood-based HIV-1/2 antigen-antibody 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-IM, HIV testing should also include an HIV RNA test prior to the first injection (and prior to starting oral cabotegravir if oral lead-in dosing is used). For person starting lenacapavir-SQ, a baseline HIV RNA test should also be ordered, but the results can be pending when starting lenacapavir. Confirming a negative baseline HIV test prior to starting HIV PrEP is extremely important—if a person had undiagnosed HIV and started on an HIV PrEP, the HIV PrEP regimen 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. Serologic 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 minor 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 HIV PrEP medications.[34] Persons with active hepatitis B can receive HIV PrEP, but upon discontinuation of HIV 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.[35]
- **Hepatitis C**: For persons who are starting HIV PrEP, baseline screening for hepatitis C virus (HCV) infection should be performed for all MSM 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.[36]

- **Pregnancy Testing**: For women of childbearing age who are starting on HIV PrEP, a baseline pregnancy test should be performed.

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 HIV PrEP will identify some persons who are nonimmune to hepatitis B; these individuals should receive a complete hepatitis B vaccine series.[37] In addition, hepatitis A immunization is recommended for certain populations that may overlap with persons seeking HIV PrEP, including MSM and persons who inject drugs.[38] Persons seeking HIV 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.[37,39] Individuals with an 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.[40] 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 HIV PrEP in combination with other effective HIV prevention methods.[10] When HIV 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 (MSM)

- **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 men who have anal sex with other men.[41] The study enrolled a total of 5,387 persons in the United States and Canada.[41] 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.[41]
- **HPTN 083**: The HPTN 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 adults at risk of acquiring HIV (mostly men who have sex with men).[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 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.[17]
- **IPreX**; The HIV 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 adult men who have anal sex with men.[20] Participants were randomly assigned to receive a daily oral dose of tenofovir DF-emtricitabine or placebo. This study documented 44% fewer new HIV infections among those who received daily tenofovir DF-emtricitabine for HIV PrEP when compared to those who received placebo.[20] 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).[20]
- **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 adult men who have anal sex with other men.[22] After a median follow-up of 9.3 months, the relative risk reduction in HIV infection was 86% in persons taking on-demand tenofovir DF-emtricitabine arm.[22]
- **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.[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 relative risk reduction in HIV infection in the immediate arm (participants who took tenofovir DF-emtricitabine daily) was 86%.[21]
- **PURPOSE 2**: In the PURPOSE 2 study, lenacapavir-SQ administered every 6 months was compared with daily oral tenofovir DF-emtricitabine in populations that predominantly consisted of men who have sex with men. Among the 2,179 participants in the lenacapavir-SQ study group, there were 2 new HIV infections, which corresponded with a 96% reduction in HIV incidence compared with the background expected HIV incidence.[42] In addition, the HIV incidence was 89% lower with lenacapavir-SQ than with oral tenofovir DF-emtricitabine.[42]

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 daily oral tenofovir DF, daily oral tenofovir DF-emtricitabine, or daily oral placebo for the prevention of HIV acquisition.[23] The partners with HIV had a median CD4 count of 495 cells/mm^3 and were not receiving antiretroviral therapy (because they were not eligible per local treatment guidelines that existed at the time the study was conducted).[23] 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.[23]
- **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.[24] In this study, daily oral use of tenofovir DF-emtricitabine resulted in a 62% reduction in HIV acquisition when compared with placebo.[24] Adherence by pill count was 84% in both medication groups.

Women

- **FEM-PEP**: 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.[43] Participants were seen at monthly follow-up visits, and the study drug was discontinued among women who became pregnant during the trial.[43] 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.[43] Adherence was low in this trial, with detectable plasma drug levels in less than 50% of the women assigned to tenofovir DF-emtricitabine.[43]
- **HPTN 084**: The HPTN 084 study was a phase IIb/3, randomized, double-blind trial to compare long-acting injectable cabotegravir-IM with daily oral tenofovir DF–emtricitabine for the prevention of HIV infection in women at risk for acquiring HIV.[18] 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 cabotegravir-IM every 8 weeks.[18] 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-IM arm. Long-acting injectable cabotegravir-IM demonstrated superior efficacy, as compared with tenofovir DF-emtricitabine for the prevention of HIV in women.[18]
- **PURPOSE 1**: In the PURPOSE 1 trial, long-acting injectable lenacapavir-SQ, administered every 6 months, was compared with oral tenofovir DF-emtricitabine and oral tenofovir alafenamide-emtricitabine.[44] Lenacapavir was 100% effective in preventing HIV acquisition among African women (0 new HIV infections); the incidence of HIV among participants who took lenacapavir-SQ was significantly lower than background HIV incidence and lower than seen with participants in the other study arms (oral tenofovir-DF-emtricitabine and oral tenofovir alafenamide-emtricitabine).[44]
- **VOICE**: The Vaginal and Oral Interventions to Control the Epidemic (VOICE) study was a randomized, placebo-controlled trial that enrolled women of reproductive age 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.[45] A total 5,029 participants were enrolled at 15 sites in South Africa, Uganda, and Zimbabwe.[45] 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.[45]

People who Inject Drugs (PWID)

- **Bangkok Tenofovir Study (BTS)**: 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.[25] All participants also received access to addiction support services, methadone programs, bleach for cleaning needles, condoms, and primary care medical services.[25] 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.[25]

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 at about 7 days, and cervicovaginal tissues at about 20 days.[46,47,48] 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.[49] The IAS-USA HIV 2022 Guidelines 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 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] There are no guidelines regarding how long it would take to achieve protection against HIV acquisition after initiating cabotegravir-IM for HIV PrEP. The IAS-USA HIV 2022 Guidelines 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] The time to protection after initiating lenacapavir is not known, but limited pharmacokinetic unpublished data from a phase 1 trial in 14 healthy adults suggest protection is likely 2 hours after taking the second oral loading dose of lenacapavir (on day 2).[50]

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.[4,51,52] 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 4).[53] 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.[20] 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.[23]. Similarly, poor adherence has correlated with a lack of HIV PrEP benefit as shown in the FEM-PrEP and VOICE trials.[43,51] 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.[54] 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.[2]

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

Key Components of Oral HIV PrEP Medication Adherence Counseling

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

Source:

- Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. December 2021:1-108. [CDC]

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); every 2–4 months for those taking long-acting injectable cabotegravir; and every 3–6 months for persons taking lenacapavir-SQ. In addition, persons receiving cabotegravir-IM 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, many 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 HIV 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 cabotegravir-IM or lenacapavir-SQ.

- **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 and persons who inject drugs.
- **Sexually Transmitted Infections (STIs)**: For MSM, screening for bacterial STIs (chlamydia, gonorrhea, and syphilis) should occur at least every 3-6 months if taking oral HIV PrEP or lenacapavir-SQ and at least every 4 months if receiving injectable cabotegravir. For heterosexually active women and 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 NAAT and include all appropriate body sites based on reported sexual activity.
- **Pregnancy Testing**: For women who might become pregnant while taking HIV PrEP, pregnancy testing should be performed at least every 3 months. If a woman becomes pregnant (or is breastfeeding) while taking HV PrEP, the clinician prescribing HIV PrEP should have a discussion with the woman 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 cabotegravir-IM for HIV PrEP and acquires HIV, the HIV genotypic resistance testing should include an integrase resistance assay (the integrase genotype typically requires a separate order from the standard genotype).[55] It is extremely important to order the resistance testing prior to starting antiretroviral treatment for HIV.
- **Initiating Antiretroviral Treatment Regimen**: Once a diagnosis of HIV is made, it is important to promptly initiate a fully suppressive HIV regimen.[10] The antiretroviral regimen can be modified, if needed, when the results from the genotype become available.[56] In general, if a person acquires HIV and has current or recent exposure to oral HIV PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine) or lenacapavir-SQ, the antiretroviral treatment should consist of a potent integrase inhibitor-based regimen: bictegravir-tenofovir alafenamide-emtricitabine or dolutegravir in combination with either tenofovir alafenamide-emtricitabine or tenofovir DF-emtricitabine.[56] If, however, a person acquires HIV and has current or prior exposure to cabotegravir-IM, the recommended initial antiretroviral therapy regimen is boosted darunavir plus either tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine. The boosted darunavir can be switched to an integrase inhibitor if the integrase genotype confirms no resistance.[56]
- **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, cabotegravir-IM, or lenacapavir-SQ, large HIV PrEP trials have reported low rates of developing HIV resistance when taking HIV PrEP.[17,23,57,58] 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.[57] In the Partners PrEP study, 5 of 63 (7.9%) seroconverters in the active HIV 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.[58] In the cabotegravir HPTN 083 study, resistance to integrase strand transfer inhibitors 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.[17] In the PURPOSE 2 trial, 2 of the 2,179 participants in the lenacapavir-SQ arm acquired HIV and both had a N74D capsid mutation.[42] Taken together, available data suggest that HIV drug resistance can occur at a significant rate in persons taking oral HIV PrEP, but this risk is reduced if baseline HIV infection is stringently ruled out prior to starting HIV PrEP and persons taking HIV PrEP have regular HIV testing.

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.[9] In some instances, however, individuals who acquire HIV while taking HIV 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 medications will only partially suppress 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 HIV 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 cabotegravir-IM, 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. At this time, standard HIV drug resistance testing does not include information on capsid resistance; information on capsid resistance would not alter the standard recommended choices for initial integrase-based antiretroviral regimen. .

Adverse Effects of Medications Used for HIV PrEP

Adverse Effects with Tenofovir DF-Emtricitabine

In several large studies in which tenofovir DF-emtricitabine was used for HIV PrEP, the medication was well tolerated and safe. The most common side effects reported in the HIV PrEP studies were nausea and decreased appetite, primarily occurring in the first month of taking the drug (sometimes referred to as “start-up syndrome”).[5,49] 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 HIV PrEP were either similar to or only slightly more common than with placebo, and resolved with discontinuation of the medication.[59,60,61] 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.[49] 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.[62,63,64,65] Findings from a recent study suggested the minor losses in bone mineral density that occurred in persons receiving HIV PrEP were recovered within 12 to 18 months after stopping PrEP.[66] 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.[41] 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.[9,41].

Cabotegravir-IM

Among persons receiving cabotegravir-IM, the most common adverse effect is injection site reactions, which resulted in the discontinuation of cabotegravir in about 2% of persons receiving this medication.[17] In the cabotegravir HPTN 083 study, among persons who experienced an injection site reaction, the most common symptoms were pain (61%) and tenderness (24%).[17] Injection site reactions typically begin about 1 day after the injection and last about 3 days.[17] 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 (antiinflammatory medications and acetaminophen) can help to alleviate symptoms.

Lenacapavir-SQ

Among persons receiving lenacapavir-SQ, injection site reactions can occur as an immediate-onset inflammatory reaction or delayed long-lasting subcutaneous nodular reaction.[42,44] The immediate-onset reactions manifest within several hours (up to 48 hours) after the injection and are characterized by pain, swelling, and erythema. [42,44] The delayed long-lasting reactions usually begin to develop several days after the injection; these reactions are characterized by subcutaneous nodes and typically persist for 6–12 months.[17] Most injection site reactions do not cause discontinuation of lenacapavir-SQ. Pre- and post-injection ice packs applied at the injection site can help to reduce the immediate onset reactions, but there are no known measures to prevent the long-lasting nodular reactions.

Changes in Sexual Practices Among Persons Receiving HIV 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.[67,68] 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.[69,70] In contrast, a systematic review did not find conclusive evidence that taking HIV PrEP leads to an increase in risky sexual activities.[71] The evidence in HIV PrEP clinical trials for risk compensation has been mixed.[23,24,25,67,72,73] 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. [74] Persons receiving HIV PrEP should also be offered doxycycline postexposure prophylaxis (DoxyPEP), which significant reduces the risk of bacterial STIs.[75]

Discontinuing HIV 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 HIV 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 HIV PrEP.
- For an individual planning to discontinue oral HIV PrEP (tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine), the protection from HIV infection will wane within several days after stopping the medication.
- 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.
- When cabotegravir-IM is discontinued, levels of the medication may remain in tissues for a year or longer (up to 4 years in some individuals).[76] If a person discontinues cabotegravir-IM, 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-IM dose. In addition, all persons stopping cabotegravir-IM should have quarterly follow-up visits that include HIV testing for at least 12 months after the last injection of cabotegravir-IM.
- If a person discontinues lenacapavir-SQ, the levels of this medication may remain for at least 12 months. Therefore, if a person discontinues lenacapavir-SQ, but has an ongoing risk of HIV acquisition, oral HIV PrEP should be recommended as a high priority during the lenacapavir “tail period,” which can last 1 year or longer.
- 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 HIV PEP to HIV PrEP

Indications for Transition from Nonoccupational HIV PEP to HIV PrEP

All persons who receive one or more courses of HIV nonoccupational postexposure prophylaxis (PEP) and have ongoing or anticipated near-future risk of 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 HIV PEP.

Timing of the Transition from Nonoccupational HIV PEP to HIV PrEP

For persons receiving nonoccupational HIV PEP who are candidates to receive HIV PrEP, the transition from nonoccupational HIV PEP to HIV PrEP should occur without any gap in protection for HIV infection (i.e., the transition should be immediate from the completion of 28 days of HIV PEP to initiation of HIV PrEP on the subsequent day).[9,10,77] 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 HIV 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 oral HIV PrEP (a 2-drug oral regimen) or long acting injectable medication (cabotegravir-IM or lenacapavir-SQ). This risk, however, appears to be very low, especially if adherence is good with occupational HIV PEP and if baseline HIV testing is performed prior to the actual transition.

Evaluation when Transitioning from Nonoccupational HIV PEP to HIV PrEP

The following clinical and laboratory evaluation is recommended when transitioning an individual immediately from nonoccupational HIV PEP to HIV 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 HIV PEP to HIV PrEP, a follow-up visit will be needed at the completion of the 28-day nonoccupational HIV 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 HIV 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 HIV PrEP at the 28-day visit while the results are pending, with the plan to immediately convert the HIV 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 HIV PrEP (or while on HIV PrEP) confirms HIV infection, the individual will need prompt evaluation for the management of newly acquired HIV.

HIV PrEP Uptake

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) women.[14,78,79,80,81,82,83]

- **HIV PrEP Uptake by Sex:** Recent surveillance data from the CDC for 2021 indicate that among persons at risk for acquiring HIV, 34% of men who could benefit from HIV PrEP were prescribed HIV PrEP compared to 12% among women.[15] A large study in the United States that evaluated HIV-seronegative, nonpregnant women who were 15 to 64 years of age found that HIV PrEP prescription rates were less than 0.5% for women who underwent HIV testing for HIV.[84] In this same study, the investigators also reported that HIV PrEP was not prescribed for more than 13,000 women who were diagnosed with gonorrhea or syphilis.[84] A retrospective analysis following 13,906 insured persons who were prescribed HIV PrEP in a large United States health care system found women, when compared with men, were less likely to receive and initiate HIV PrEP and more likely to discontinue HIV PrEP once it was started.[85]
- **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%).[15] The reasons for these differences are complicated and likely involve many factors, including access to care.
- **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.[15]

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 a once-yearly injectable lenacapavir-IM and oral or injectable islatravir (a nucleoside reverse transcriptase translocation inhibitor).[86,87] Novel delivery systems, such as microarray patches, vaginal films, implants (including ultra-long-acting, refillable implants), and others, are also in development.[88] 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.[89,90] The future for HIV PrEP medications is likely to include a greater array of medication and delivery system options.

Summary Points

- 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 regimens (tenofovir DF-emtricitabine and oral tenofovir alafenamide-emtricitabine) and long-acting injectable medications (cabotegravir-IM and lenacapavir-SQ). Note that tenofovir alafenamide-emtricitabine is not indicated for women or other individuals whose risk factor for HIV acquisition is receptive vaginal sex.
- A baseline laboratory evaluation, including baseline HIV testing, is required prior to starting HIV PrEP.
- Laboratory monitoring 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 while receiving 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 HIV PrEP clinical trials.
- The risk of developing HIV drug resistance associated with HIV PrEP can occur, but this risk is lowered if appropriate HIV testing is done at baseline and at regular time intervals.
- If an individual with chronic hepatitis B infection is taking HIV PrEP, discontinuing tenofovir DF-emtricitabine or tenofovir alafenamide-emtricitabine could lead to a serious hepatitis B flare.
- Transitioning from nonoccupational HIV PEP to HIV PrEP optimally involves an immediate transition without a gap.
- When discontinuing HIV PrEP, repeat HIV testing should always be performed, and the reason for discontinuation should be documented in the health record.

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Figures

Figure 1 Estimated HIV Incidence in United States, 2018-2022

Source: Centers for Disease Control and Prevention. Estimated HIV Incidence and Prevalence in the United States, 2018–2022. HIV Surveillance Supplemental Report. 2023;29(1). Published May 2024.

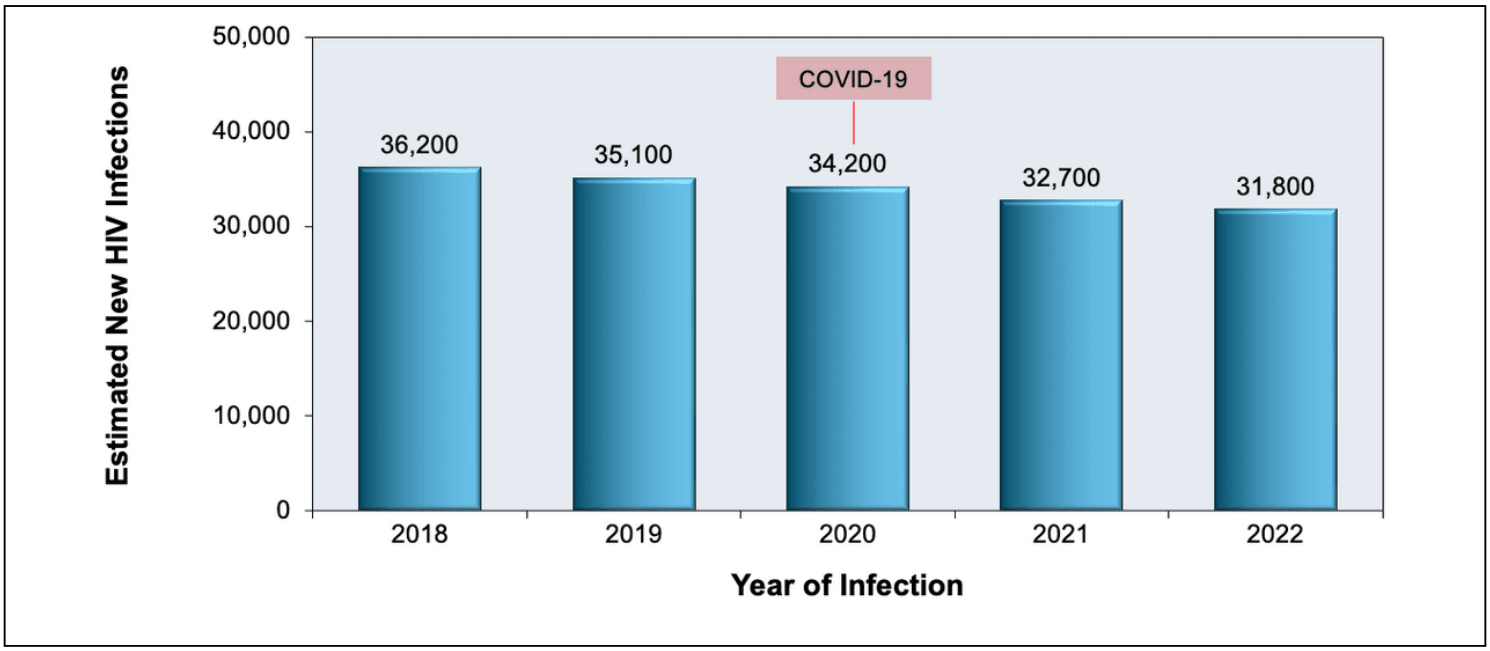

Figure 2 (Image Series) - Basic Concepts for Types of HIV PrEP (Image Series) - Figure 2 (Image Series) - Basic Concepts for Types of HIV PrEP
Image 2A: Daily Oral HIV PrEP

Illustration: David H. Spach, MD

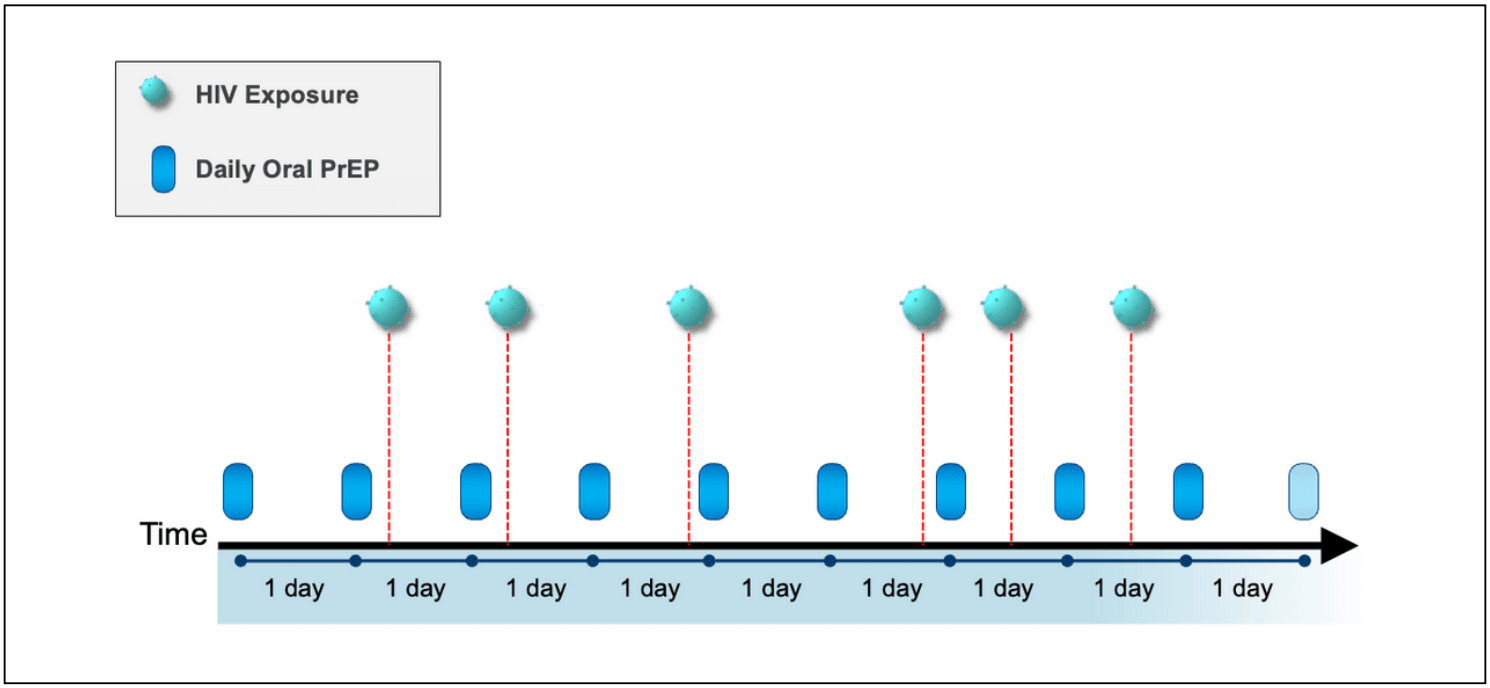

Figure 2 (Image Series) - Basic Concepts for Types of HIV PrEP
Image 2B: On-Demand (2-1-1) Oral HIV PrEP

Illustration: David H. Spach, MD

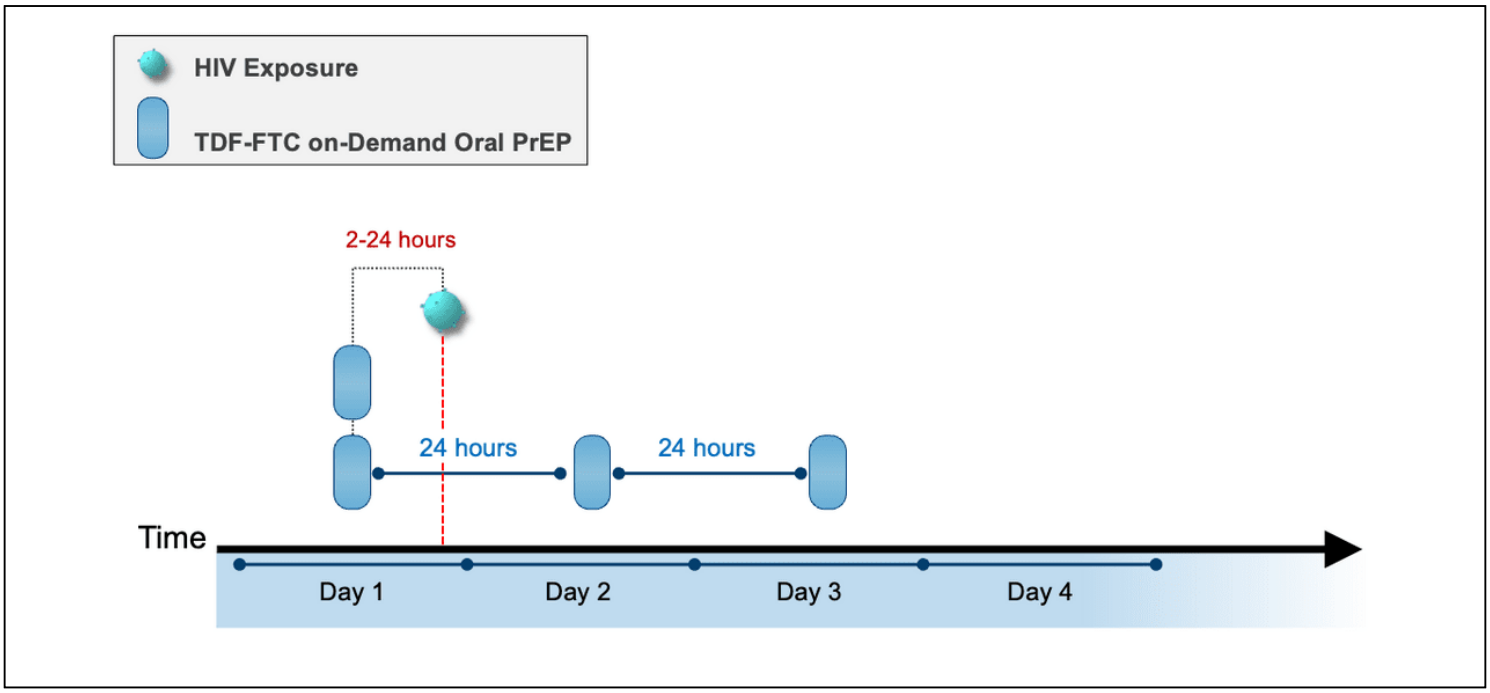

Figure 2 (Image Series) - Basic Concepts for Types of HIV PrEP
Image 2C: Long-Acting Cabotegravir-IM for HIV PrEP

Illustration: David H. Spach, MD

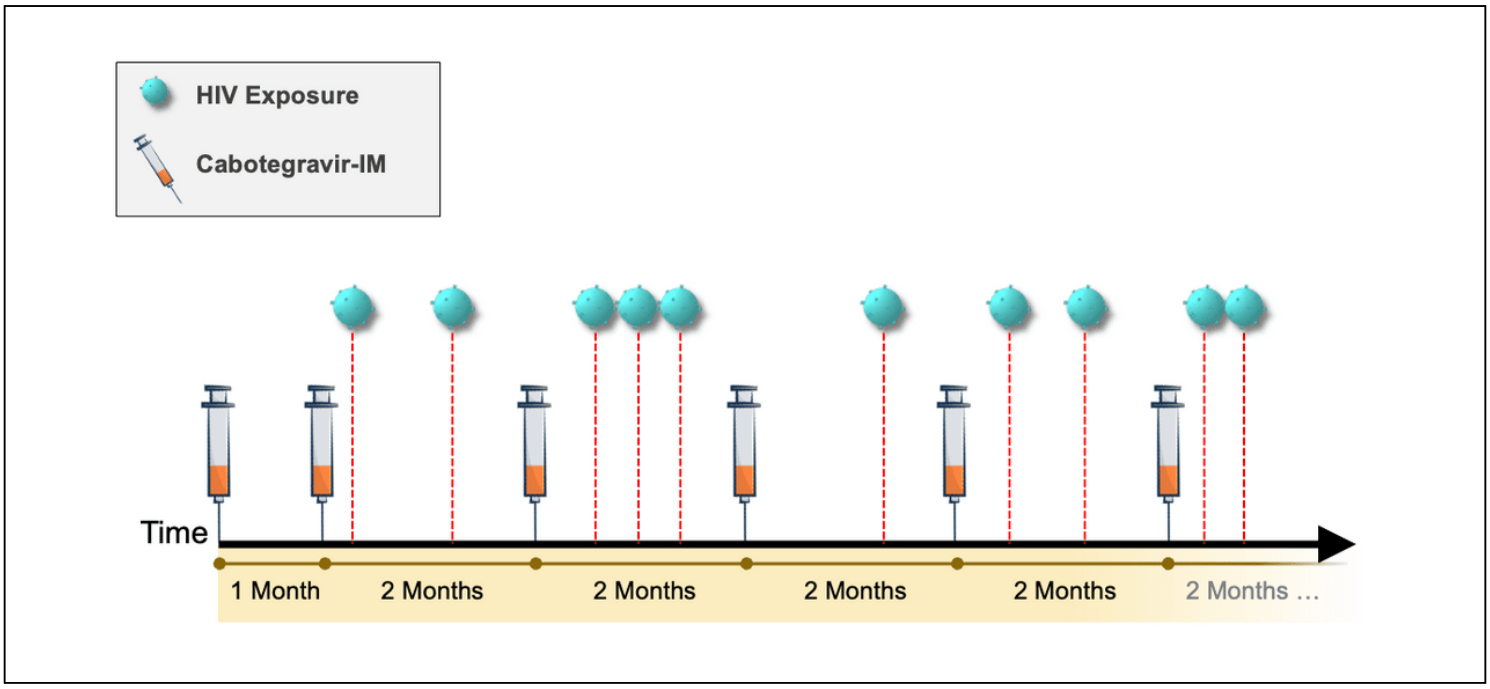

Figure 2 (Image Series) - Basic Concepts for Types of HIV PrEP
Image 2D: Long-Acting Lenacapavir SQ for HIV PrEP

Illustration: David H. Spach, MD

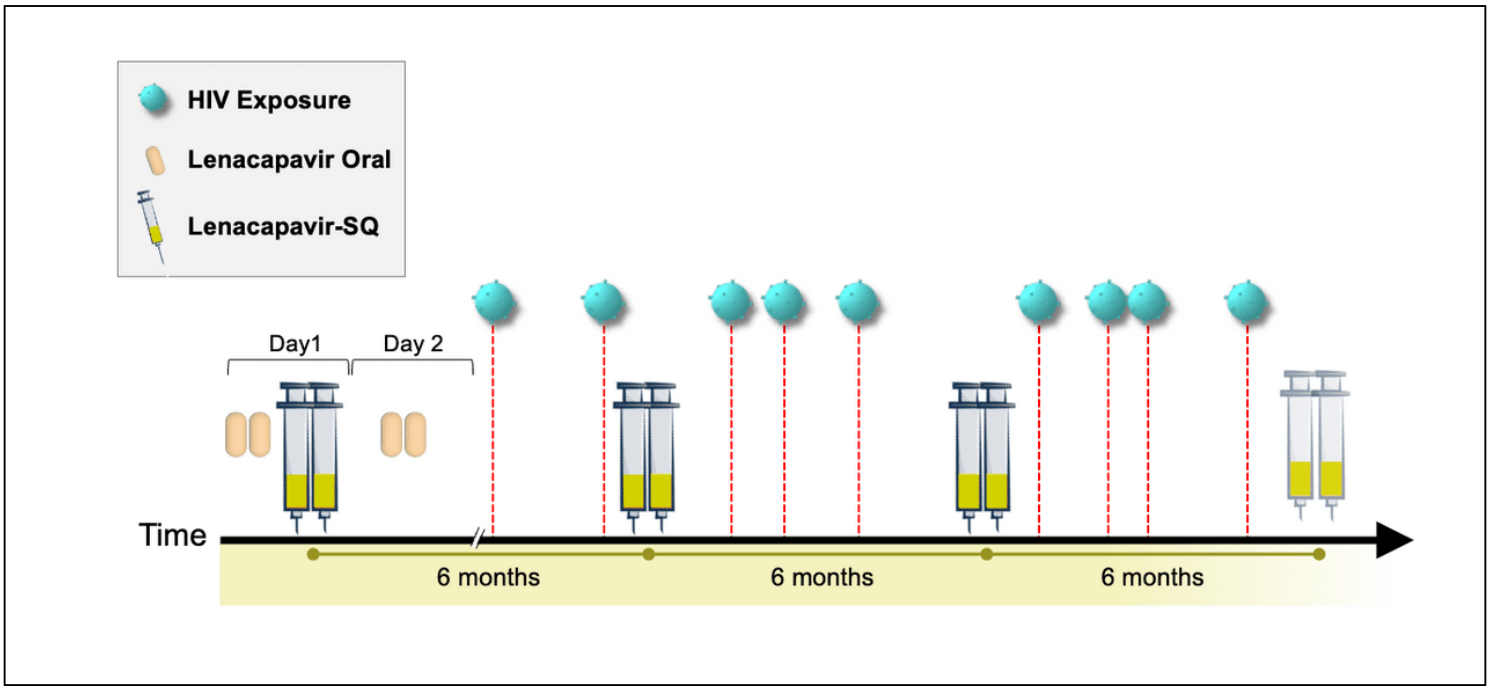

Figure 3 HIV PrEP Coverage, United States, 2017-2022

Source: (1) Centers for Disease Control and Prevention. Monitoring Selected National HIV Prevention and Care Objectives by Using HIV Surveillance Data United States and 6 Dependent Areas, 2021. HIV Surveillance Supplemental Report. 2023;28(No. 4):1-138. Published May 2023. (2) U.S. Health and Human Services. America's HIV Epidemic Analysis Dashboard (AHEAD). PrEP Coverage.

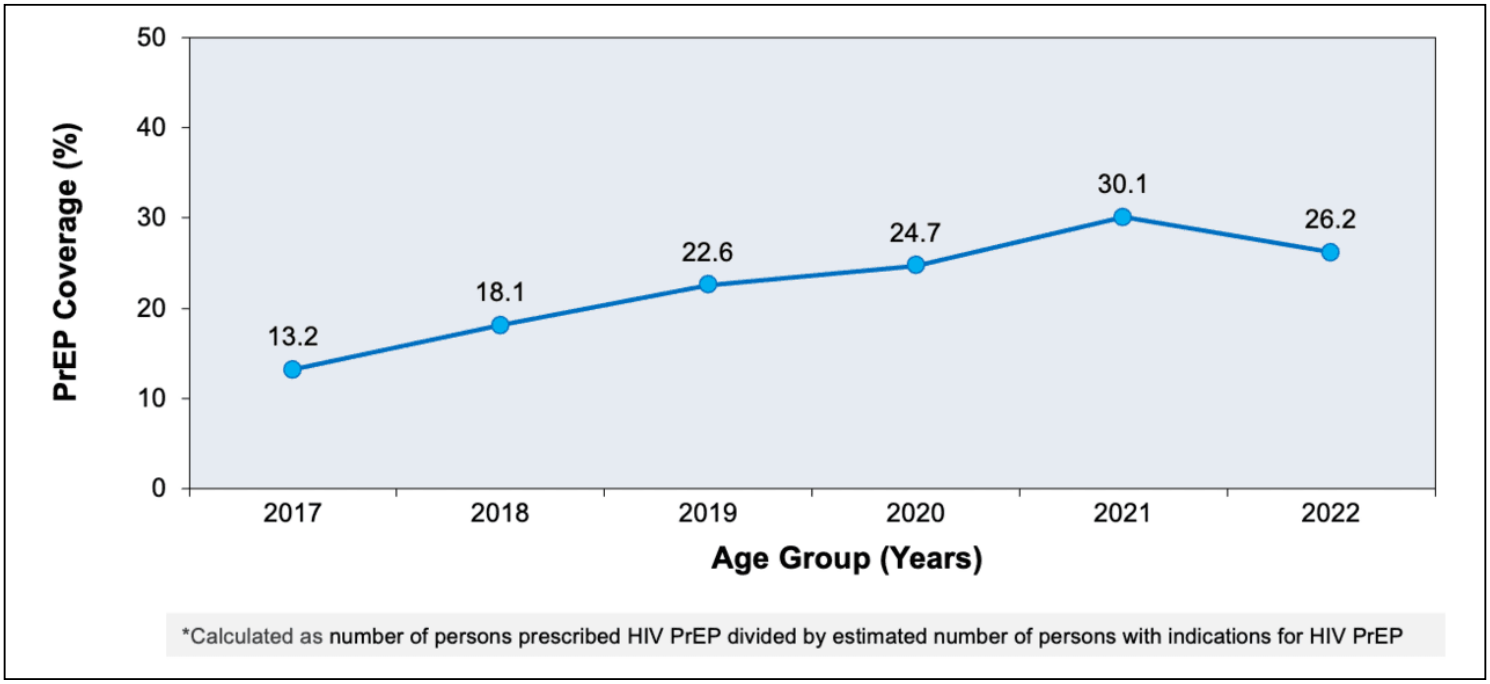

Figure 4 Estimates of PrEP Efficacy Adjusted for Adherence

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.

Source: Marrazzo JM, del Rio C, Holtgrave DR, et al. HIV prevention in clinical care settings: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA. 2014;312:390-409.

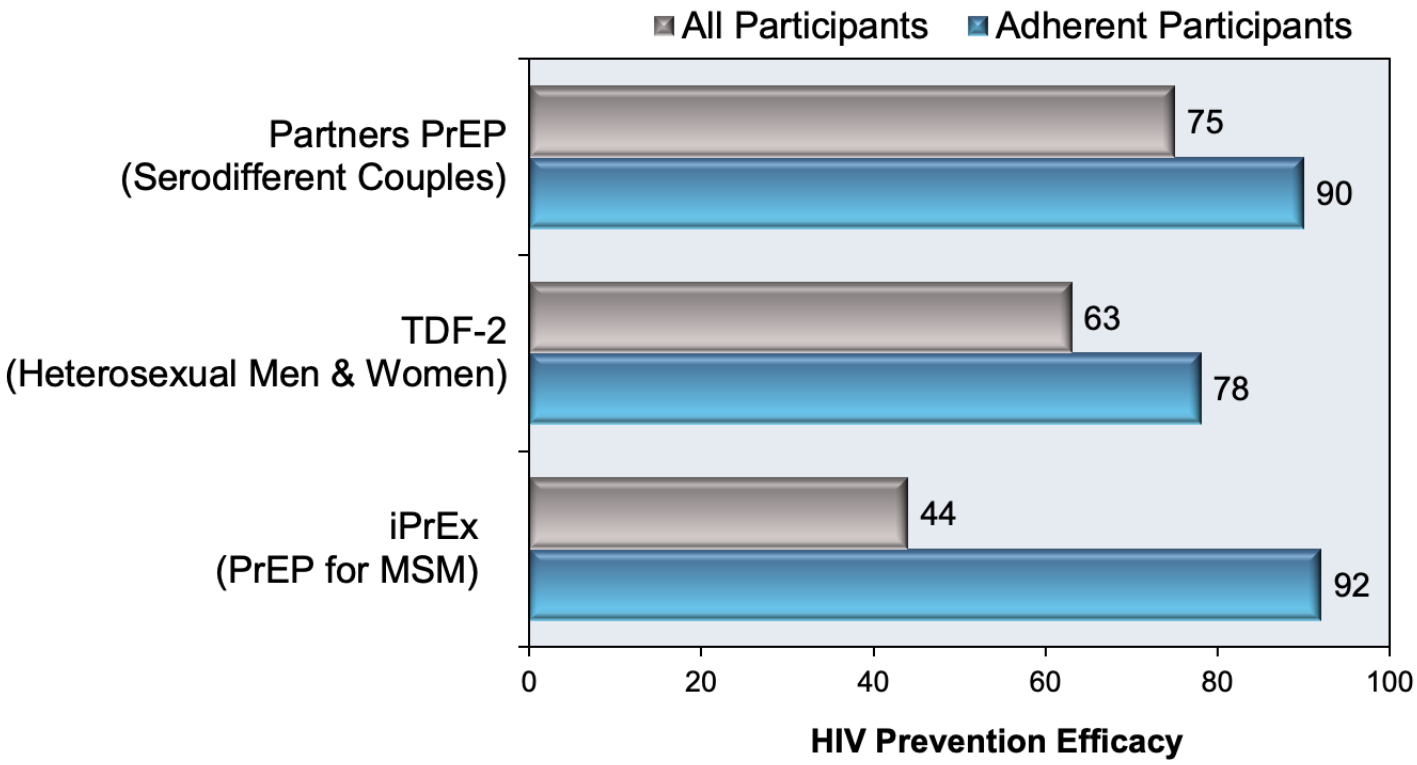

Table 1. **USPHS: Preexposure Prophylaxis for the Prevention of HIV Infection in the United States**

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

Source:

- Centers for Disease Control and Prevention: US Public Health Service: Preexposure prophylaxis for the prevention of HIV infection in the United States—2021 Update: a clinical practice guideline. December 2021:1-108. [CDC]