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Initiating pre-exposure prophylaxis: What primary care providers should know

Abstract: Pre-exposure prophylaxis (PrEP) is an HIV preventive service and treatment that is continuing to evolve. With the availability of in-house lab screenings and simplified testing protocols, primary care providers are in a unique position to initiate and provide the added layer of HIV protection for their patients.

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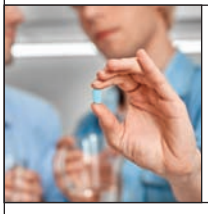
It is estimated that 1.2 million people living in the US have HIV, with approximately 14% of these individuals unaware that they are infected.[1] While the annual number of new diagnoses has decreased by 7% from 2014 to 2018, infection rates have remained stagnant for varying age groups.[2] It is important to utilize every tool available to lower new HIV infections. The primary care clinician is a vital source in reducing the overall HIV burden. Along with other methods of prevention, pre-exposure prophylaxis (PrEP) can be an important tool in HIV prevention.

Epidemiology

In 2018, approximately 38,000 individuals were diagnosed with HIV in the US.[1] Estimates suggest that

Keywords: HIV; HIV prevention; pre-exposure prophylaxis; PrEP; primary care

without intervention, roughly 400,000 new individuals will be diagnosed with HIV in the US over the next 10 years.[3] While any individual can contract HIV, rates of infection vary by groups. The age group with the highest infection rate in 2018 was 25-34 years, followed by 35-44 years.[1] In terms of race/ethnicity, Black Americans had the highest rate of HIV infection in 2018, followed by Hispanics.[1] Individuals who are born male have higher HIV infection rates compared with those born female.[1] By region, the South has the highest number of individuals with new HIV infections while the Northeast has the highest rate of people living with HIV.[1,2] Finally, HIV transmission is highest for those individuals who engage in male-to-male sexual contact. This accounts for 69% of new infections in the US.[1]



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Pathophysiology of HIV

HIV is an enveloped retrovirus that attaches to the CD4 molecule and a chemokine receptor allowing it to enter T lymphocytes.[4] After attachment and penetration, viral replication occurs through reverse transcriptase causing mutations that facilitate resistance to the host's immune system and antiretroviral drugs.[4] Such penetration of T lymphocytes damages the immune system, resulting in depletion of T lymphocytes and inability to fight infection.[4] The continued spread of HIV throughout the body's immune system leads to a decreased response to infections, allowing for opportunistic infections, and eventually progression to AIDS.[4]

Risk factors

Individuals who participate in high-risk behavior are strong candidates for the initiation of PrEP. High-risk behavior can constitute those with multiple sexual partners, men who have sex with men (MSM) and participate in anal sex without a condom, or those who have been diagnosed with a sexually transmitted infection (STI) within the past 6 months.[5,6] Additional high-risk behavior includes I.V. drug use and sex with those who are HIV-positive.[5,6]

What is PrEP?

PrEP is a once-a-day pill regimen recommended for people not infected with HIV who participate in behavior that is high-risk for exposure to HIV.[7] Within the US, two medications are currently approved for PrEP, 1) emtricitabine (FTC) 200 mg and tenofovir disoproxil fumarate (TDF) 300 mg (abbreviated as F/TDF; brand name, Truvada), and 2) emtricitabine (FTC) 200 mg and tenofovir alafenamide (TAF) 25 mg (abbreviated as F/TAF; brand name, Descovy).[7] Both medications consist of a combination of anti-HIV drugs within a single pill that is taken once a day with or without food.[7] F/TDF and F/TAF can reduce the risk of becoming infected with HIV from sex by 99% when taken as prescribed, excluding receptive vaginal sex for which F/TAF is not indicated.[8,9] Additionally, PrEP can reduce the risk of HIV for individuals who inject drugs by at least 74% when taken as prescribed.[8] Currently, F/TDF is recommended for all adults and adolescents who weigh at least 35 kg and are at risk for HIV through sex or injection drug use by the CDC.[8] Comparably, F/TAF is recommended for adults and adolescents at risk for HIV through sex and who weigh at least 35 kg, but not for those who engage in receptive vaginal sex.[8,10] Currently, F/TAF is not indicated to prevent HIV infection in individuals engaging in receptive vaginal sex.[9]

PrEP mechanism of action

While many different medications with varying mechanisms of action are approved for the treatment of HIV, only FTC, TDF, and TAF classified as nucleoside reverse transcriptase inhibitors (NRTIs) are currently approved within the US for PrEP.[11] The NRTI class blocks the reverse transcriptase process within host T lymphocytes. This prevents the formation of a new DNA chain, thus inhibiting the first replication cycle and preventing infection.[11]

Drug interactions

As with many medications used in practice today, drug interactions can occur with PrEP drugs that prescribers should be aware of. Medications that compete for active tubular secretion and renally eliminated drugs have the possibility to increase FTC concentration.[9] Some common medications eliminated by

active tubular secretion include acyclovir, valacyclovir, aminoglycosides, and high-dose nonsteroidal anti-inflammatory drugs.[9] Alternatively, protease inhibitors (tipranavir/ritonavir), antiepileptic drugs (carbamazepine, oxcarbazepine, phenytoin, phenobarbital), antimycobacterials (rifabutin, rifampin, rifapentine), and herbal products (St. John's wort) can reduce the concentration of TAF and are not recommended for coadministration.[9] Finally, TDF concentrations can be increased or decreased by or can affect levels of certain antiviral medications often used for the treatment of HIV or hepatitis C.[10] As with prescribing any medication, the provider should use any references available to help discern possible medication interactions as a comprehensive list of interactions is beyond the scope of this article.

Adverse reactions to PrEP

A clear discussion is needed with the patient regarding the possible expected adverse reactions from taking PrEP before initiation to ensure commitment to taking the medication daily. The most common adverse reactions to PrEP are nausea, which occurred in 4% to 5% of participants; diarrhea, 5% to 6%; abdominal pain, 2% to 4%; vomiting, 2%; fatigue, 2% to 3%; headache, 2% to 7%; and weight loss, 3%.[9,10,12] These adverse reactions did diminish over time, most within a few weeks, but there is no specific resolution time frame reported in the current literature.[13] PrEP can cause kidney and liver damage in some individuals, along with lactic acidosis.[12,14] PrEP can cause a decrease in the estimated glomerular filtration rate (eGFR).[15] One study showed reduction in eGFR by 2 to 3 mL/min/1.73 m^2 after a 36-month F/TDF regimen, with this change being reversed 4 weeks after discontinuation.[15] Overall, the reduction in renal function was small and reversible but can be higher in those with a history of renal disease and concurrently taking nephrotoxic drugs.[15] Liver damage and subsequent lactic acidosis has been associated with TDF when used among patients who are HIV-positive on long-term therapy but has shown low rates when used for PrEP.[16] Additionally, patients with hepatitis B infection should not stop PrEP treatment without having a discussion with their primary care provider as medication discontinuation could lead to a severe acute hepatitis B exacerbation.[12,14] A boxed warning has been issued concerning stopping PrEP therapy in a patient infected with hepatitis B with instruction to monitor hepatic function closely for several months after discontinuation.[10] Currently, research is limited on the effects of PrEP use on the fetus during pregnancy.[10,17] F/TDF is an option for those who are at risk for HIV and who are pregnant; however, a full discussion of considerations for this topic is outside the scope of this article.[10,17] Prescribers are encouraged to review relevant references for more information.[13,17,18] A discussion on pregnancy intent is integral with every individual with reproductive potential before initiation of PrEP. F/TDF also has an additional warning of bone loss that could contribute to osteoporosis.[12]

Signs and symptoms of acute HIV infection[12,21]

Fever	Headache
Rash	Sore throat
Myalgia	Fatigue
Night sweats	Lymphadenopathy
Arthralgia	Diarrhea

Requirements for initiation of PrEP

The introduction of PrEP requires that individuals be screened and tested for underlying conditions before the initiation of medication. A requirement for the use of PrEP is that an individual be negative for HIV because of the possibility of development of drug-resistant HIV variants with the use of these medications for PrEP in patients who have HIV. However, it's possible the course of infection could be too early for testing to be accurate. Due to this possibility, the individual should be assessed for signs and symptoms of acute HIV infection (see *Signs and symptoms of acute HIV infection*). In the presence of these signs and symptoms, PrEP initiation should be deferred until testing can be completed and acute HIV infection dismissed.[17] All patients, regardless of whether they are symptomatic or not, need to have a documented negative HIV blood test prior to PrEP

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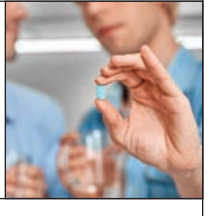


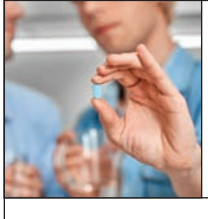
Suggested lab requirements for PrEP initiation and monitoring[17]

Lab Test	Initial Visit	1 Month	3 Months	6 Months	9 Months	12 Months
HIV	✓	✓	✓	✓	✓	✓
Pregnancy	✓	✓	✓	✓	✓	✓
Renal function*	✓		✓		✓	
STI**	✓		✓	✓	✓	✓
Hepatitis B	✓					✓
Hepatitis C	✓					✓

*after testing at 3 months, may taper down to once every 6 months if no concerns arise while on PrEP
**may be once every 3 or 6 months, depending on patient factors

initiation. Additionally, for individuals intending to begin the PrEP process, willingness to take the prescribed PrEP medication as directed with adherence to the follow-up appointment and testing schedule should also be determined. A candid discussion can assist in limiting nonadherence, failure to prevent HIV, and drug resistance.[17]

Once screening for signs and symptoms of acute HIV infection and willingness to adhere to the prevention regimen is completed, lab screening can be initiated (see *Suggested lab requirements for PrEP initiation and monitoring*). HIV testing is required prior to PrEP initiation. When selecting an HIV test, an antigen (Ag)/antibody (Ab) (preferably fourth generation) blood test is preferred with an Ab-only or rapid blood test also being acceptable.[17] No oral fluid testing is acceptable for PrEP initiation as it can have lower sensitivity than blood tests.[17] If an Ab-only or rapid test is used to determine HIV status, PrEP can be initiated but it should be confirmed with Ag/Ab testing.[17]



In addition to the required lab screening for the initiation of PrEP, a sexual history should also be included in initiation and follow-up discussions.

Screening for hepatitis B and C should also be completed prior to PrEP initiation, with referral to a specialist being recommended if the individual has either or both infections. Hepatitis B testing should be conducted and immunization offered to those who test negative for hepatitis B surface antibody, hepatitis B surface antigen, and total anti-hepatitis B core.[17] Renal function testing (including serum creatinine, estimated creatinine clearance, urine glucose, urine protein, and, for patients with chronic kidney disease, serum phosphorus) is needed.[9,10,17] F/TDF for PrEP should not be initiated or used with a creatinine clearance less than 60 mL/minute.[10,17] F/TAF can be used in patients with creatinine clearance of 30 mL/minute or greater but prescribers should refer to the F/TAF package insert for more details on use in patients with renal impairment.[9] Pregnancy testing and screening for STIs is also required with subsequent treatment of infection according to current guidelines.[17]

In addition to the required lab screening for the initiation of PrEP, a sexual history should also be included in initiation and follow-up discussions. Taking a sexual history not only assesses those individuals at high risk for HIV infection but also provides intervention, which can motivate a behavioral change.[19] By interviewing the individual and having them recall sexual history and encounters, awareness of past exposure and the consequences of engaging in risky behavior can be discussed.[19] This discussion can help advise the individual against risky behavior to reduce not only exposure to HIV but other infections as well.[19] While taking a sexual history can be difficult due to patient and provider discomfort and time limitations, incorporating this topic in routine practice is important for the overall health and risk reduction for the individual.[17,19]

Prescribing, follow-up visits, and education

To ensure effectiveness, PrEP should be initiated as quickly as possible after a negative HIV lab screening has been completed to limit the possibility of exposure between the initial visit and lab sample drawing to actual initiation of medication.[17] Same-day labs are optimal for the initiation of PrEP but starting the medication within a week once labs are available is reasonable.

Following the initial visit, providers may wish to have a follow-up visit within a month to discuss adverse reactions, difficulties with medication adherence, and to answer any questions.[17] Subsequent follow-up visits should be scheduled every 3 months to coincide with HIV testing. Patients should be given a 90-day prescription when possible to prevent interruption, but no more than a 90-day supply should be given due to the need for continued testing.[17] Each visit should assess adverse reactions, adherence, current risk behaviors, and counseling on risk reduction and the importance of continuing PrEP for HIV prevention.[17] Follow-up HIV and pregnancy testing should be conducted every 3 months, along with screening for signs and symptoms of acute HIV infection. STI testing for chlamydia, gonorrhea, and syphilis should occur at least every 3 months for MSM who are at high risk for recurrent bacterial STIs and for those with signs or symptoms of infection, and testing for syphilis and gonorrhea should occur for all people on PrEP every 6 months as should testing for chlamydia for MSM, unless earlier testing is warranted.[17] Follow-up renal function testing should be conducted initially at 3 months and then may be extended to every 6 months if no concerns arise while on PrEP.[17]

Counseling and education should be provided to individuals so that PrEP can help reduce and prevent the risk of HIV infection. However, PrEP will not prevent other STIs. Therefore, emphasizing the use of condoms as part of any sexual activity is important. Additionally, education regarding the time frame for PrEP to become effective is needed with every initiation. PrEP will reach maximum protection in approximately 7 days for those individuals participating in receptive anal sex.[8] Those participating in receptive vaginal sex and/or injection drug use and taking F/TDF will attain maximum protection in approximately 21 days.[8] Currently, no data are available on time to maximum effectiveness for those individuals participating in insertive anal or insertive vaginal sex.[8]

Implications for practice and future directions

The initiation and continuation of PrEP in the primary care setting provides vital and much-needed services to patients. While the overall rate of new diagnoses of HIV has decreased within the US, many high-risk groups have not seen any progression in case reduction.[2] Primary care providers being on the front lines of the medical system can significantly impact the rate of HIV in the US by identifying and preventing infection in individuals at high risk. PrEP is a significant tool in the prevention of HIV and has the ability to save individuals from a lifelong infection with no current cure.

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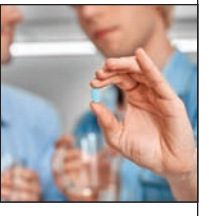

The future of HIV prevention with PrEP is hopeful with an array of new methods being reviewed and analyzed. Currently, long-acting injectable forms of PrEP are being studied and have shown promise in clinical trials.[20] These injectable forms and other new oral medications will allow individuals and providers choices on tailoring HIV prevention to the patient, lowering barriers to effective treatment, improving adherence, and reducing additional HIV infections.

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The authors and planners have disclosed no potential conflicts of interests, financial or otherwise.

DOI-10.1097/01.NPR.0000757076.21006.50