Pre-Exposure Prophylaxis (PrEP) to Prevent HIV During Periconception, Antepartum, and Postpartum Periods

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Panel's Recommendations
• Centers for Disease Control and Prevention (CDC) guidance recommends health care providers should discuss PrEP with all sexually active people without HIV—including individuals who are trying to conceive, pregnant, postpartum, or breastfeeding—to prevent HIV acquisition (AII); counseling should include the benefits of PrEP to prevent HIV acquisition and perinatal transmission (AI) and potential adverse effects of PrEP during periconception, pregnancy, postpartum, and breastfeeding periods (AII). Health care providers should offer PrEP to those who desire PrEP or have specific indications for PrEP use (e.g., injection drug use). • Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is currently the U.S. Food and Drug Administration (FDA)-approved PrEP option for HIV prevention with known safety and efficacy data in people with receptive vaginal exposure and with demonstrated safety in pregnancy. People who become pregnant while using TDF/FTC as PrEP can continue PrEP throughout their pregnancy. Risk for HIV acquisition should be reassessed, and people should be counseled regarding benefits and risks of PrEP use in pregnancy (AII). • Long-acting injectable cabotegravir (CAB-LA) is FDA approved for people with vaginal exposure to HIV. For people with PrEP indications in pregnancy, CAB-LA dosing, efficacy, and safety remain unknown. If a person receiving cabotegravir (CAB) PrEP becomes pregnant, the limited available safety data and long half-life of CAB should be discussed with the patient with shared decision-making, and the patient may benefit from expert consultation. • Providers should counsel patients about the importance of daily adherence to oral TDF/FTC PrEP to prevent HIV acquisition (AI). Patients should be counseled to use additional HIV prevention strategies (e.g., condoms) for the first 20 days after initiating TDF/FTC PrEP and for 28 days after last potential vaginal exposure (BII). No available data support on-demand PrEP when HIV exposure occurs through vaginal exposure. • Providers should offer routine PrEP follow-up, including testing for HIV every 3 months and counseling on signs and symptoms of acute retroviral syndrome (AI) (see the CDC's PrEP for the Prevention of HIV in the United States—2021 Update and Maternal HIV Testing and Identification of Perinatal HIV Exposure). More frequent testing may be appropriate when clinically indicated (e.g., adherence challenges, nonstandard visit schedule). • In cases when the individual has a partner with HIV and that partner is on antiretroviral therapy with sustained viral suppression, condomless sexual intercourse is associated with no risk of sexual HIV transmission when HIV viral load is suppressed (AI) (see Reproductive Options for Couples When One or Both Partners Have HIV).
Rating of Recommendations: A = Strong; B = Moderate; C = Optional *Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion*

HIV PrEP is the use of specific antiretroviral (ARV) drugs to prevent HIV acquisition. The use of combination tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) as daily oral PrEP to reduce HIV acquisition was approved by the U.S. Food and Drug Administration (FDA) in 2012. When taken as prescribed, TDF/FTC provides greater than 90% protection against acquiring HIV. The HIV Prevention Trials Network (HPTN) 084 found cabotegravir (CAB) to be 89% more effective than TDF/FTC.[1] Susceptibility to HIV acquisition is greater during the periconception period, throughout

pregnancy, and through 6 months postpartum. Acute or recent HIV infection during pregnancy or breastfeeding is associated with an increased risk of perinatal HIV transmission, see Early (Acute and Recent) HIV Infection.[2,3] The Panel on Treatment of HIV Infection During Pregnancy and Prevention of Perinatal Transmission (the Panel) recommends that people without HIV who are planning to have a child or who are pregnant, postpartum, or breastfeeding should be routinely counseled about PrEP for HIV prevention and offered PrEP or referred for PrEP care services when indicated to prevent HIV acquisition and potential perinatal HIV transmission.[4]

Most research on PrEP cited in this section was conducted with participants who self-identified as women (presumed to be predominantly cisgender women). However, patients who do not identify as women (i.e., transgender men, genderqueer or nonbinary individuals) can become pregnant, give birth, and breast/chestfeed. PrEP should be offered and promoted for all individuals with an indication for PrEP using a gender-affirming approach to care (see Transgender People with HIV in the Adult and Adolescent Antiretroviral Guidelines).

Of the FDA-approved PrEP medication for people with receptive vaginal exposure, TDF/FTC is currently the only option with demonstrated safety and efficacy in pregnancy. The guidance in this section focuses on the use of TDF/FTC as PrEP during periconception, antepartum, and postpartum periods (through 6 months postpartum and/or throughout breastfeeding).

What Is Known About Other PrEP Agents During Periconception, Antepartum, and Postpartum Periods?

Long-acting injectable CAB (CAB-LA) is FDA approved for use as PrEP in adults and adolescents. Limited data from HPTN 084 on the pharmacokinetics of CAB-LA in women who stopped CAB once pregnancy was diagnosed show CAB decline was within the expected limit for non-pregnant women.[5-7] A similar study in pregnant women receiving CAB-LA and rilpivirine for ARV treatment reported that the tail was within expected range for non-pregnant women.[8,9] However, because data on the pharmacokinetics of CAB injections continued during pregnancy are not available, it is not known whether the dosing interval for non-pregnant individuals needs modification during pregnancy. Although there are no prospective safety data in pregnancy among people who continued CAB, CAB has structural similarities to other ARVs (e.g., dolutegravir) for which there are reassuring safety profiles in pregnancy. The remainder of pharmacokinetic (PK) and safety data in pregnancy are from animal models. CDC guidance notes that CAB for PrEP may be initiated or continued in people who become pregnant while receiving injections when the anticipated benefits outweigh the risks. There are also limited data on neonatal outcomes of *in utero* CAB exposure.[5,8,9] For people with PrEP indications who are planning for pregnancy, the optimal time to conceive after stopping injections is unknown.

CDC guidance notes that CAB for PrEP may be initiated or continued in people who become pregnant while receiving injections when anticipated benefits outweigh the risks. For people with PrEP indications in pregnancy, as CAB dosing, efficacy, and other details are still unknown, TDF/FTC is preferred for initiation during pregnancy given the more robust safety and efficacy data.[10-13] If a person receiving CAB PrEP becomes pregnant, the limited available safety data and long half-life of CAB should be discussed with the patient and the patient and provider should engage in shared decision-making. Expert consultation may be beneficial to make the best decision

about continuing or discontinuing CAB PrEP in light of evolving data and knowledge. Important considerations include the following:

- Given the long half-life of injectable CAB, exposure at start of pregnancy is likely to continue throughout the pregnancy (thus the benefit of stopping CAB at pregnancy is uncertain).
- CAB has structural similarities to other ARVs (e.g., dolutegravir) for which there are reassuring safety profiles in pregnancy.
- If CAB is stopped during pregnancy and HIV exposure is ongoing, alternative strategies for HIV prevention should be offered (e.g., TDF/FTC PrEP).

Clinicians are encouraged strongly to register people who become pregnant while receiving CAB with the Antiretroviral Pregnancy Registry.

Dapivirine vaginal ring also reduces the risk of HIV acquisition via receptive vaginal exposure but is not FDA approved and not recommended in pregnancy due to lack of approval and limited safety data during conception, pregnancy, and breastfeeding. Oral tenofovir alafenamide (TAF)/FTC has not yet been demonstrated to be effective for HIV prevention in people with receptive vaginal exposure.

Clinical Management of PrEP Use During Periconception, Antepartum, and Postpartum Periods

Initiating and Stopping PrEP

The Centers for Disease Control and Prevention (CDC) has issued guidelines (see PrEP for the Prevention of HIV in the United States—2021 Update) to discuss PrEP with all adults and adolescents who have sex or inject drugs.[14] The Panel recommends that PrEP be discussed with all persons without HIV who are planning for pregnancy and/or sexually active and those who are pregnant or postpartum. PrEP can be prescribed to those who request it and is also specifically indicated for individuals who—

- Have a history of bacterial sexually transmitted infection (STI)[15,16];
- Have infrequent condom use with one or more partners of unknown HIV status, especially within a high-prevalence sexual network;
- Are taking non-occupational post-exposure prophylaxis (nPEP) and anticipate ongoing indications for prevention or have used multiple courses of nPEP[17];
- Engage in transactional sex;
- Have substance use disorder and/or substance use associated with sex;
- Have a partner with HIV without consistent virologic suppression;
- Have a history of experiencing intimate partner violence[18]; or
- Have a partner with any of the factors listed above.

Providers should counsel people with HIV whose partners may have indications for PrEP about benefits and indications for PrEP. When prescribing PrEP, clinicians should inform patients that:

- TDF/FTC is FDA approved for those weighing at least 35 kg.
- Counsel patients about potential risks and benefits of PrEP and all available strategies for reducing HIV acquisition risks during periconception, antepartum, and postpartum periods, including the use of PrEP for safer conception (see Reproductive Options When One or Both Partners Have HIV). People who become pregnant while using TDF/FTC PrEP can continue PrEP throughout their pregnancy.
- Explain that condomless sex with a partner who has sustained viral suppression is associated with no risk of HIV sexual transmission.[19-22]
- Although it is unknown how long PrEP needs to be taken before a person can be considered protected from vaginal HIV exposure, or how long it needs to be continued after last exposure, conservative guidance is to take daily oral TDF plus FTC for 20 days before considering an individual fully protected and to continue it for 28 days after last exposure.[4] (Time to protection for CAB is not known.)
- Prescribe TDF/FTC as a once-daily, fixed-dose combination tablet whenever possible. Provide counseling about the importance of adherence and suggest adherence supports, such as use of a pillbox (see Adherence Support below).
- Counsel that episodic or on-demand PrEP has not been shown to be effective for vaginal exposure.
- Counsel individuals who are taking PrEP about the symptoms associated with acute HIV infection and instruct them to contact their provider immediately for HIV testing and further evaluation if symptoms occur (see Early (Acute and Recent) HIV Infection). Patients experiencing symptoms of acute HIV infection should be instructed to use a condom during sex, stop attempts at conception, and stop breastfeeding.
- PrEP does not protect against other STIs. Condom use is important for reducing risks of STI acquisition.
- Regularly assess and discuss ongoing needs for PrEP.
- Inquire about partner status and offer partner HIV testing
- Additional prescribing details, including for same day PrEP start and PrEP follow-up via telehealth, are offered in the CDC Guidelines for PrEP (see PrEP for the Prevention of HIV in the United States—2021 Update).[14]

Indications for PrEP use may change across the course of periconception, antepartum, and postpartum periods. Even after the postpartum period, HIV vulnerability may remain. In addition, people may have repeat pregnancies and, therefore, ongoing discussion regarding the possibility of pregnancy (planned or unplanned) and the need for PrEP should continue.

Contraception

Contraception is an important component of reproductive health care for people receiving PrEP who do not want to become pregnant.[19] No known significant drug–drug interactions exist between TDF and different modes of hormonal contraception used during periconception and the postpartum period.[23-25] For additional information, refer to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2016 and the Update to U.S. Medical Eligibility Criteria for Contraceptive Use,

2016: Updated Recommendations for the Use of Contraception Among Women at High Risk for HIV Infection regarding use of contraception by women at high risk of HIV infection.

Laboratory Testing

Recommended laboratory testing for individuals receiving PrEP includes—

- HIV diagnostic testing with an antigen/antibody combination immunoassay at baseline. For people exposed to antiretrovirals as PrEP, delays can be seen in antigen/antibody detection during acute infection.[26] Therefore, the CDC recommends antigen/antibody combination immunoassay as well as HIV-RNA testing every 3 months, or more frequently if indicated based on clinical symptoms, for people taking tenofovir-containing PrEP regimens.
- HIV testing for individuals taking PrEP during pregnancy should include HIV testing at entry into antenatal care, with re-testing in the second and third trimester. More frequent testing may be appropriate when clinically indicated (e.g., known adherence challenges) (see Maternal HIV Testing and Identification of Perinatal HIV Exposure).
- If HIV is documented in people receiving PrEP, they should be referred immediately to an HIV specialist, start on antiretroviral therapy (ART), and receive appropriate care to prevent perinatal transmission if pregnancy has occurred.
- Renal function testing is recommended at baseline and then every 12 months for persons <50 years of age and/or with estimated creatinine clearance (CrCl) over 90 mL/min. Otherwise, renal function should be monitored every 6 months. TDF/FTC as PrEP should not be initiated in patients with a confirmed calculated CrCl <60 mL/min. Clinicians should discontinue daily TDF/FTC as PrEP if a patient develops a confirmed calculated CrCl <50 mL/min.
- Testing for hepatitis B virus (HBV) infection should be performed for patients initiating PrEP, but PrEP initiation need not be delayed while awaiting results. Individuals with no prior HBV infection who lack HBV immunity should be vaccinated if they have not received HBV vaccination or consider reimmunization if they have been vaccinated but still lack immunity. Individuals with chronic HBV should be counseled regarding the risk for possible hepatitis flares when tenofovir-based PrEP is stopped.[27]
- Pregnancy testing should be completed at baseline and then as indicated for those who can become pregnant.
- Testing for STIs (gonorrhea, chlamydia, syphilis) is recommended at baseline. Testing every 6 months is recommended for gonorrhea and syphilis for women. Annual testing for chlamydia is also recommended.
- Additional information and details about recommended laboratory testing is available in the CDC's PrEP for the Prevention of HIV Infection in the United States—2021 Update. Clinicians are encouraged strongly to register people who become pregnant while receiving PrEP with the Antiretroviral Pregnancy Registry.

Time to Protection

Adherence is particularly important to achieve effective drug concentrations in vaginal and cervical tissues and may be even more important in the second and third trimesters of pregnancy, when drug levels drop because of expanding volume of distribution and increased renal clearance. Studies in

nonpregnant women demonstrate that it may take up to 20 days to reach maximum intracellular concentrations of tenofovir and/or FTC in cervicovaginal tissue, compared to only 7 days in anal tissues.[28-30] Although pharmacokinetic data are limited in pregnant women, data suggest that pregnant women taking daily PrEP experience lower tenofovir drug levels; it remains unknown what drug level or number of pills per week correlates with protection for this population.[31,32] The available data are limited, and the CDC guidelines suggest 20 days are needed to achieve protective levels in cervicovaginal tissues. Given the increased volume of distribution and concomitant lower levels of TDF/FTC in plasma, the Panel recommends continued use of other prevention strategies until PrEP has been taken for at least 20 days and protection against transmission can be assumed in pregnant or postpartum PrEP users. Six to seven doses a week (or daily dosing) are needed to maintain drug levels in cervicovaginal tissue in nonpregnant women. When people initiate PrEP and have not yet reached protective drug levels or struggle with daily adherence, other strategies should be used to prevent HIV.

Adherence Support

Before initiating PrEP, providers should assess barriers to PrEP adherence and address concerns regarding PrEP use during the periconception, antepartum, and postpartum periods. The decision to initiate PrEP should be reached using a shared decision-making process, and opportunities to promote adherence and mitigate barriers adherence should be addressed at each visit. Data suggest that some adherence challenges stem from adherence fatigue, low personal perceptions of risk, stigma, cost, misinformation about PrEP, peer perspectives, mental health challenges, and intimate partner violence.[33-35] Based on barriers, providers can discuss strategies tailored to each patient's needs to promote adherence and maximize benefits. Approaches include providing accurate information about the risks and benefits of PrEP, developing reminder strategies, and identifying supportive individuals as part of the health care team or the patient's social network who can provide social support toward PrEP adherence. Just like HIV care, PrEP ideally should be delivered in a comprehensive manner and address social determinants of health—including how clients will make sure that PrEP and related services are affordable—and address housing instability, access to health insurance, and transportation because these factors have been shown to interfere with adherence. CDC provides a PrEP webpage and a PrEP chapter.

Background on Use of PrEP During Periconception, Antepartum, and Postpartum Periods

Women account for nearly 20% of new HIV diagnoses in the United States, most via heterosexual transmission, yet only account for 7% of people prescribed PrEP.[36,37] PrEP is recommended for all people with potential exposure to HIV.[4,38] Although data about the use of PrEP among periconception, pregnant, and postpartum people are less robust than for nonpregnant people, PrEP is highly efficacious for women, and a large body of data from pregnant women using TDF/FTC as treatment for HIV and HBV suggests these agents are safe for pregnant and breastfeeding women and their infants.[12,13,39,40]

Susceptibility to HIV acquisition is greater during periconception, antepartum, and early postpartum periods through 6 months. Data suggest that people trying to conceive are at higher risk for HIV acquisition, likely due to increased condomless sex.[41,42] The increase in HIV acquisition risk continues in pregnancy and is likely due to a combination of behavioral factors—such as no longer needing to use condoms for contraception—and biological factors that include increased innate and suppressed adaptive immunity, increased genital tract inflammation, alterations in the

vaginal microbiome, decreased integrity of the vaginal epithelium, and both gross trauma and microtrauma to the genital tract during delivery.[43-45] HIV incidence among women during pregnancy and postpartum is two to six times greater than outside of pregnancy.[45-49] Two large HIV prevention studies conducted in African countries demonstrated that the probability of HIV acquisition per condomless sex act increases beginning in early pregnancy and peaks in the early postpartum period (in data analyzed from birth through 24 weeks postpartum in most studies). After adjustment for age, use of PrEP, and male partner HIV viral load, the probability of HIV acquisition was significantly higher throughout pregnancy and the postpartum period (adjusted relative risk 2.76; 95% CI, 1.58–4.81).[50] In addition, people who acquire HIV while pregnant or breastfeeding are more likely to transmit HIV to their infant.[51-53]

Despite the risks of HIV acquisition and known efficacy of PrEP,[12,39,40] PrEP remains vastly underutilized among women,[54,55] especially during pregnancy and breastfeeding. The American College of Obstetricians and Gynecologists[38] and the World Health Organization[56] agree that all HIV prevention options, including PrEP, should be encouraged for people with HIV vulnerability, especially during pregnancy and breastfeeding, given the increased risk of HIV acquisition during pregnancy and the potential for perinatal transmission with seroconversion during pregnancy. For people with a sexual partner who is taking ART and virally suppressed, the risk of HIV acquisition is effectively zero.[19-21] However, because viral suppression can be variable and not all people with HIV remain in care or maintain effective adherence, some partners of people with HIV may choose to use PrEP.[57] People who inject drugs during pregnancy and postpartum also should be offered PrEP for prevention.[4,38,58] Updated CDC guidance suggests that PrEP should be discussed with all adolescents and adults who are sexually active which may include those who are planning for pregnancy.[14]

Efficacy of TDF/FTC as PrEP During Periconception, Pregnancy, and Postpartum Periods

Data from two randomized controlled trials that enrolled heterosexual-identifying men and women demonstrated the efficacy of TDF/FTC as PrEP to be 63% to 75%. In women with detectable drug levels (or taking PrEP), PrEP protected against 90% of incident transmissions.[59] In a meta-analysis of all available clinical trial data, modeling suggested that if women adhere to at least 75% of doses, PrEP decreases HIV acquisition by 61% (relative risk 0.39; 95% CI, 0.25–0.60).[60]

Although people planning for pregnancy were not enrolled in these clinical trials, subsequent data from demonstration projects suggest that PrEP uptake and adherence are high during periconception periods. In Kenya, 74 HIV-serodifferent couples—including 40 women without HIV—enrolled into a safer conception study. In the month preceding pregnancy confirmation, 81% of partners who were HIV negative were highly adherent to PrEP.[61] In South Africa, 526 individuals (334 women and 192 men) from 334 partnerships were enrolled in a study to promote safer conception care. PrEP was initiated as part of safer conception care by 51% (n = 22) of women without HIV in this study. No sexual or perinatal HIV transmission events were observed.[62] In a small cohort of U.S. women using PrEP to prevent HIV infection during the periconception period, adherence was excellent, with 87% having intracellular tenofovir levels consistent with protection.[63,64]

Safety of TDF/FTC as PrEP for Women, Including Those Who Are Pregnant or Breastfeeding

Efficacy trials of TDF/FTC as PrEP excluded women who reported plans to become pregnant and/or were pregnant, but abundant data are available from (a) PrEP use during early pregnancy among women who are HIV negative, due to inadvertent exposure in clinical trials (e.g., pregnancy occurred and the study drug was discontinued once pregnancy was detected); (b) PrEP use during periconception, pregnancy, and breastfeeding from demonstration projects that included pregnant women and those planning for pregnancy; (c) tenofovir use during late pregnancy for HBV treatment in women who are HIV seronegative; and (d) use of tenofovir and FTC as ART by pregnant women with HIV. These data all indicate that TDF/FTC PrEP is safe for use during pregnancy.

A 2017 systematic review of 26 studies involving TDF and FTC exposure during pregnancy did not identify safety concerns that would limit the use of PrEP in pregnant or lactating women or require discontinuation of PrEP in women who become pregnant while still at continuing risk of HIV acquisition.[13] In 2020, an additional systematic review examined five completed studies that included 1,042 TDF/FTC PrEP-exposed pregnancies.[65] Four of the five studies did not observe differences in pregnancy or perinatal outcomes associated with TDF/FTC exposure. One study did find that TDF/FTC PrEP-exposed infants had a lower z-score for length at 1 month of age; however, no difference was observed at 1 year. These studies all come from subanalyses of clinical trials. Because pregnant women were excluded from these trials, most of the data regarding TDF/FTC PrEP exposure reflect early first-trimester exposures. The authors also noted that at least nine ongoing studies, soon to be completed, will provide data on more than 6,200 additional TDF/FTC PrEP-exposed pregnancies and will assess perinatal, infant growth, and bone health outcomes. Currently available data suggest that the benefits of TDF/FTC as PrEP to prevent HIV outweigh any potential toxicities. PrEP should be promoted as an HIV prevention strategy during periconception, pregnancy, and postpartum periods.

Additional data and primary sources describing what is known about TDF and FTC on birth outcomes, renal and bone effects for women, and renal and bone effects for infants exposed to TDF/FTC *in utero* or while breastfeeding are available in the Tenofovir Disoproxil Fumarate (Viread, TDF) and Emtricitabine (Emtriva, FTC) sections of these guidelines.

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