PrEP ME CONTRA COSTA

PrEP FAQs for Providers

1. WHAT IS PrEP?

PrEP stands for pre-exposure prophylaxis. It is the use of antiretroviral medication to prevent acquisition of HIV infection. PrEP is used by HIV uninfected people who are at risk of being exposed to HIV through sexual contact or injection drug use. At present, the only medication with an FDA-approved indication for PrEP is oral tenofovir disoproxil fumarate-emtricitabine (TDF-FTC), which is available as a fixed combination tablet called **Truvada.** This medication is also commonly used in the treatment of HIV.

PrEP should be considered part of a comprehensive prevention plan that includes adherence, risk reduction counseling, HIV prevention education and provision of condoms.

2. WHAT ARE THE GUIDELINES FOR PRESCRIBING PrEP?

Two sets of guidelines for prescribing PrEP exist:

- Contra Costa County Public Health Guidelines [1] - which focuses on the identification of individuals at highest risk for HIV who would be ideal candidates for PrEP
- Centers for Disease Control (CDC) Guidelines [2], including a Clinical Providers' Supplement [3]

Find both sets of guidelines at https://cchealth.org/hiv/prep/providers.php

The Clinical Providers' Supplement contains additional tools for clinicians providing PrEP, such as a patient/provider checklist, patient information sheets, provider information sheets, a risk incidence assessment, supplemental counseling information, billing codes and practice quality measures.

If PrEP questions arise, clinicians should consult the PrEP line.

University of California, San Francisco
Clinician Consultation Center Line.
University of California San Francisco (CCC)
Line 1-855-448-7737
Monday—Sunday
6am–5pm PST
This line is available for clinicians only.

3. TO WHOM SHOULD I OFFER PrEP?

Per CDC Guidelines, PrEP may be appropriate for the following populations:

MEN WHO HAVE SEX WITH MEN	HETEROSEXUAL WOMEN & MEN	INJECTION DRUG USERS
• HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work	• HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • Person living in high-prevalence area or network	• HIV-positive injecting partner • Sharing injection equipment • Recent drug treatment (but currently injecting)

Per Contra Costa Guidelines, clinicians should also discuss PrEP with the following non-HIV- infected individuals (other than those mentioned above):

- Male-to-female and female-to male transgender individuals engaging in condomless anal intercourse with men
- Individuals who report the use of mood-altering substances during sex (e.g. alcohol, methamphetamine, cocaine, ecstasy, poppers etc.)
- MSM or transgender people engaging in condomless anal receptive sexual intercourse
- Transgender people engaging in transactional sex, providing sex in exchange for money or drugs
- Diagnosis of urethral gonorrhea or rectal chlamydial infection within the prior 12 months
- Persons seeking a prescription for PrEP (as they may be at high risk of HIV acquisition but uncomfortable providing a full sexual history to the provider)
- Individuals who have been prescribed PEP for non-occupational exposures and demonstrate continued high-risk behavior, or have used multiple courses of PEP, among men who have sex with men (MSM).

4. WHO CAN PRESCRIBE PREP?

Any licensed prescriber can prescribe TDF-FTC as PrEP. Specialization in Infectious Disease or HIV Medicine is NOT required. In fact, primary care providers who see members of populations at high risk of HIV on a routine basis should consider offering PrEP to all eligible patients.

5. HOW IS TDF-FTC FOR PREP PRESCRIBED?

TDF-FTC for oral PrEP is taken once daily by mouth. No other dosing strategy is currently recommended.

PrEP should be discontinued immediately if: (1) the patient becomes HIV-infected, or (2) the patient experiences toxicities or symptoms that cannot be managed. Condoms and supportive counseling, both for adherence and risk reduction, are required.

1ST PRESCRIPTION:	30 days of medication (1 month without refill)
2ND PRESCRIPTION:	60 days of medication (1 month with 1 refill)*
SUBSEQUENT PRESCRIPTIONS	90 days of medication (1 month with 2 refills; each prescription must be preceded by a negative HIV test)

*HIV testing only indicated if concern for acute HIV infection exists.

6. WHAT IS THE EVIDENCE BASE FOR PrEP?

Clinical trials of oral daily PrEP show these results:

STUDY	POPULATION	N	RESULTS
iPrEX [6] *Brazil, Ecuador, Peru, S. Africa, Thailand, U.S.A*	MSM	2,499	44% efficacy TDF-FTC
Partners PrEP Study [7] *Kenya, Uganda*	Heterosexual Couples	4,758	67% efficacy TDF 75% efficacy TDF-FTC
TDF2 Study [8] *Botswana*	Young men and women	1,200	62% efficacy TDF-FTC
Bangkok Tenofovir Study (BTS) [9] *Thailand*	Injection Drug Users	2,400	49% efficacy TDF

*Overall risk reduction; intention to treat analysis.

Studies among women only are discussed in question 11.

7. HOW IMPORTANT IS ADHERENCE TO PREP?

Adherence is critical. In all PrEP clinical trials to date, PrEP efficacy appeared to depend on adherence [12, 13]. According to a dedicated analysis of adherence of those trials, PrEP was non-efficacious when adherence was low, but when moderate or high adherence was achieved, efficacy was modest or relatively high, respectively [13]. Among the study subjects with detectable plasma tenofovir levels in iPrEx, Partners PrEP, TDF2 and BTS, efficacy ranged from 74 to 92% [6, 7, 8, 9].

Adherence to PrEP was also found to be highly associated with reduction of HIV risk in an open-label study (iPrEX OLE) [14]. Among participants with drug detected by dried blood spot, HIV incidence ranged from 4.7 infections per 100 person-years (no drug detected) to 0.6 per 100 person-years (two to three tablets per week). There were no HIV infections in participants using four or more tablets per week.

Another study suggested that an "on demand" regimen (i.e., use of PrEP just before and after sex) might also reduce HIV acquisition among MSM (IPERGAY [15]), although the frequency of sexual acts among men in that study was high enough that they closely approximated four tablets weekly (which, as mentioned above, provides very high levels of protection). The effectiveness of "on demand" PrEP among those using PrEP less frequently is unknown. At this time, the only recommended PrEP dosing strategy is daily [16].

8. HOW QUICKLY DOES PrEP PROVIDE PROTECTION?

Data from pharmacokinetic studies suggest that individuals need to take PrEP for:

- At least 7 days to achieve protective levels in rectal tissue and plasma [3,17]
- At least 20 days to achieve protective levels in cervicovaginal tissue

9. IS PrEP SAFE?

TDF-FTC as PrEP is considered safe and well-tolerated. Although TDF-FTC has caused renal toxicity and decreased bone mineral density when used for HIV treatment and administered for months and years, in PrEP studies to date, TDF-FTC has not caused serious safety concerns [5, 18, 19].

PrEP is considered safe for women of child-bearing age. Available data suggest that TDF-FTC does not increase risk of birth defects, although there are not enough data to exclude the possibility of harm. TDF-FTC is considered in Pregnancy Class B. PrEP is often used in pregnancy if the risk of ongoing HIV transmission is sufficiently high (such as in a sero-different partnership) and because pregnancy itself is associated with an increased risk of HIV acquisition. Per CDC guidelines, if

pregnancy is intended in a sero-different relationship, PrEP can also be used periconceptionally by the uninfected partner to reduce the risk of sexual HIV acquisition. Expert consultation is recommended for these couples.

Since TDF-FTC is actively eliminated by the kidneys, it should be co-administered with care in patients taking medications that are eliminated by active tubular secretion (e.g., acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides and high-dose or multiple NSAIDs). Drugs that decrease renal function may also increase concentrations of TDF-FTC.

10. WHO IS NOT ELIGIBLE FOR PREP?

- HIV-positive people. Individuals must be confirmed as HIV-negative before initiating PrEP. Excluding those with acute HIV infection is critically important, as there is a risk of developing resistant HIV if they are inadvertently started on TDF-FTC as PrEP. (TDF-FTC is an appropriate component of a regimen to treat HIV, but must be combined with an additional agent from another class of antiretroviral to provide effective treatment.)
- People with renal insufficiency. Providers should confirm that the patient's calculated creatinine clearance is > 60 mL/minute (Cockcroft-Gault formula) before initiating PrEP.

Additionally, those who indicate that they are not ready to adhere to daily oral TDF-FTC should not be prescribed PrEP (since efficacy is extremely limited when patients do not adhere, as described above).

11. DOES PREP WORK IN WOMEN?

Current clinical guidelines include women as appropriate candidates for PrEP. As with all PrEP patients, adherence is critical. Two trials of PrEP in women were stopped early for futility by their respective data safety and monitoring boards [20, 21].

A determination of futility is made when it appears that no evidence of efficacy would be found in the future based on the results collected up to that point. Low adherence among the participants was thought to be a substantial factor in the futility finding. Other studies that included both men and women (TDF-2, Partners PrEP) in which higher levels of adherence were achieved did show efficacy among women. Recent data suggest that women may need higher levels of adherence than men, in order to achieve protective levels of drug in the female genital tract.

12. CAN ADOLESCENTS TAKE PREP?

PrEP is an important HIV prevention tool for adolescents. Tenofovir/Emtricitabine was approved by the FDA for PrEP in adolescents on May 15,2018 [23].

The addition of the adolescent indication is backed by a single-arm, open-label clinical trial, ATN113, conducted in HIV-negative individuals 15-17 years old by the Adolescent Medicine Trials Network for HIV/AIDS [24].

Note: Minors age 12 or older may request testing and consent to medical care related to the diagnoses and treatment of Sexually Transmitted Diseases/HIV (Cal. Family Cord 6926).

13. WHAT BASELINE ASSESSMENT IS REQUIRED FOR INDIVIDUALS BEGINNING PREP?

The most important aspect of the baseline assessment is ascertaining that the patient is not already HIV-infected. HIV testing should be conducted immediately prior to starting PrEP, ideally on the same day the prescription is provided.

Contra Costa Guidelines recommend that baseline testing should be conducted with a lab-based fourth-generation (preferred) or viral load (for a list of FDA-approved third- and fourth-generation tests, go to http://www.cdc.gov/hiv/testing/lab/guidelines).

For patients with symptoms of acute infection or for those whose antibody test is negative but who have reported condomless sex or needle-sharing in the past month, a nucleic acid amplification test (NAAT, viral load) for HIV is preferred prior to initiating PrEP.

CDC Guidelines recommend the following baseline HIV testing: baseline testing should be conducted with any HIV test other than an oral rapid test due to that test's lower sensitivity. (A whole blood rapid test is acceptable.) For patients with signs/symptoms of acute HIV infection within the prior four weeks, the following options are suggested (see algorithm on p. 33 of the CDC Guidelines):

- Retest antibody in one month; defer PrEP decision.
- Send blood for HIV antibody/antigen assay (i.e., fourth generation HIV testing). If the patient is negative, it is acceptable to initiate PrEP.
- Send blood for HIV-1 viral load (VL) assay. If the patient has VL<50,000 copies/mL, PrEP should be deferred while testing is repeated. If the VL is below the level of detection of the assay, and the patient has no signs/symptoms on that day, it is acceptable to initiate PrEP. In all other scenarios (e.g. VL>50,000, which is consistent with a diagnosis of HIV infection; signs/

symptoms present on day of blood draw, which is concerning for acute HIV infection), PrEP should be deferred.

Additionally, it is important to screen for hepatitis B virus (HBV) infection prior to starting PrEP. Those found to be susceptible to HBV (absence of Hepatitis B surface antibody, or sAb, in serum) should be offered HBV vaccination. If active HBV infection is diagnosed, TDF-FTC can be initiated for both HBV treatment and HIV prevention. Later, if TDF-FTC is discontinued for HIV prevention an alternative, treatment for active HBV must be continued to avoid a flare [25].

Emerging PrEP Initiation Strategy: Some jurisdictions start a standard PEP regimen of an integrase inhibitor (InSTI) plus TDF-FTC if acute HIV infection is suspected based on symptoms and if results of HIV NAAT testing are pending. If the NAAT test is negative, the InSTI is discontinued and TDF-FTC is continued as PrEP. If HIV viremia is detected, resistance testing is obtained and the patient it continued on the TDF-FTC plus InSTI regimen as antiretroviral therapy (ART) to treat infection (Personal communication, Dr. Matthew Golden, April 9, 2016).

14. WHAT ADDITIONAL SUPPORT AND ONGOING ASSESSMENT ARE REQUIRED FOR PATIENTS ON PREP?

As mentioned above, PrEP should be prescribed as part of a combination prevention plan. Studies of PrEP have involved substantial support, including HIV testing more frequently than recommended in real-world management, intensive adherence and risk reduction counseling, HIV prevention education and condom provision.
At minimum, while patients are on PrEP, Contra Costa County and CDC Guidelines recommend the following:

Monitoring	Frequency
Prevention and medication support	At every visit
Assess adherence	
Provide risk reduction counseling	
Offer condoms	
Laboratory testing	
HIV testing	
• Contra Costa County recommendations: Lab Based 4th generation Ag/Ab HIV test or HIV Viral Load • CDC guidelines - Any testing except oral rapid HIV testing	• Every 3 months and whenever there are of acute infection (serologic screening test and HIV RNA test)
STD Screening	
• NAAT to screen for Gonorrhea and Chlamydia. Advocate for 3 or 4-site testing: pharyngeal, rectal, urethral, and vaginal (if applicable) • Rapid Plasma Reagin (RPR) or Treponemal IgG • Inspection for anogential lesions	Screen for symptoms: • At every visit Test for syphilis • Every 3 months • Test for Gonorrhea and Chlamydia • Every 3 months, even if asymptomatic • Whenever symptoms are reported
Monitoring	Frequency
Hepatitis C antibody test	At least every 12 months for: • People who use drugs • Men who have sex with men • People with multiple sexual partners
Serum creatinine and calculated creatinine clearance	At 3 months after initiation, then every 6 months
Pregnancy testing	Every 3 months

15. WILL PREP BE COVERED FOR MY PATIENTS?

Many insurance plans cover PrEP. TDF-FTC is on the California Medi-Cal formulary. Medi-Cal completely covers the cost of TDF-FTC as PrEP as well as medical visits and laboratory testing. Prior authorization is NOT required.

Several programs have been established to help cover the cost of PrEP and associated care. Contact our PrEP Navigator at (925) 313-6771 for more information.

16. IF I TAKE CARE OF BOTH MEMBERS OF A SERO-DIFFERENT COUPLE, IS IT PREFERABLE TO TREAT JUST THE HIV-POSITIVE PARTNER, JUST THE HIV-NEGATIVE PARTNER OR BOTH?

The Contra Costa County Public Health Department and national experts recommend that all people with HIV be treated, regardless of clinical status or CD4 cell count [26, 27]. Virologic suppression of the HIV-infected partner protects his or her health and the health of the HIV-uninfected partner [28].

Whether the HIV-negative partner should take PrEP if the positive partner is virologically suppressed is a matter of substantial debate. This decision must be individualized and may depend on the HIV-positive partner's virologic control, condom use and other partners that the HIV-negative partner may have. Recent findings from a large cohort study among stable, sero-different couples where the HIV positive partner was virologically suppressed suggested that in this situation the risk of seroconversion may be negligible [29]. Reasons why PrEP might still be offered include that adherence to antiretroviral therapy can lapse, and that there can be differences between plasma and seminal/vaginal fluid viral load measurements at any one time [30]. Additionally, research suggests that most HIV transmission is from non-main partners [28].

17. CAN PREP BE USED TO HELP SERO-DIFFERENT COUPLES CONCEIVE?

PrEP may be one of several options to help protect the HIV-negative male or female partner in a heterosexual HIV sero-different couple during attempts to conceive. Expert consultation is recommended so that approaches can be tailored to specific needs, which may vary from couple to couple. In all cases, initiation of ART for the HIV-infected partner is recommended, and, once therapy is initiated, the positive partner should achieve sustained virologic suppression before conception is attempted. Extensive counseling of both members of the couple is recommended regardless of the specific approach selected. For more information, consult federal guidelines before attempting conception [31].

For more information:
Go to https://cchealth.org/hiv/prep/providers.php or email Contra Costa County Department of Public Health at prepme@hsd.cccounty.us

REFERENCES

1. Contra Costa County. PrEP Guidelines: Who Needs PrEP in Contra Costa County. 2018. https://cchealth.org/hiv/prep/providers.php
2. Centers for Disease Control and Prevention (CDC). A Clinical Practice Guideline. Pre-Exposure Prophylaxis for the Prevention of HIV Infection in the United States-2017 Update. 2017. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf
3. Centers for Disease Control and Prevention (CDC). Clinical Providers' Supplement. Pre-Exposure Prophylaxis for the Prevention of HIV Infection in the United States. 2017. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2017.pdf
4. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a clinical screening Index predictive of Incident HIV Infection among men who have sex with men In the United States. J Acquir Immune Defic Syndr. 2012;60(4):421-7.
5. Krakower D, Mayer KH. What primary care providers need to know about preexposure prophylaxis for HIV prevention: a narrative review. Annals of Internal Medicine. 2012;157(7):490-7.
6. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. The New England Journal of Medicine. 2010;363(27):2587-99.
7. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. The New England Journal of Medicine. 2012; 367(5):399-410.
8. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission In Botswana. T he New England Journal of Medicine. 2012;367(5):423-34.
9. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV Infection in Injecting drug users In Bangkok. Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo controlled phase 3 trial. Lancet 201 3;381(9883):2083·90.
10. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, Hare CB. No New HIV Infections with Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. Clin Infect Dis. 2015.
11. McCormack S, Dunn D T, Desal M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 Infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. The Lancet 2015;387(1 0013): 53-60.
12. Van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS 2012; 24;26(7): F13-9.
13. Koenig LJ, Lyles C, Smith DK. Adherence to Antiretroviral Medications for HIV. Pre- Exposure Prophylaxis: Lessons Learned from Trials and Treatment Studies. American Journal of Preventive Medicine. 2013;44(1 Suppl 2): S91-8.
14. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. The Lancet: Infectious Diseases 2014; 14(9): 820-829.
15. Molina J-M, Gapitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. The New England Journal of Medicine. 2015;373(23):2237 -2246.
16. New York City Department of Health and Mental Hygiene (NYCDOHMH). PrEP CROI Summary 2015. 2015. http://www.nyc.gov/htmVdoh/downloads/pdf/hcp/prep-croi-summary-2015.pdf.
17. Seifert S, Glidden D, Anderson P, et al. Dose Response for Starting and Stopping HIV Preexposure Prophylaxis for Men Who Have Sex with Men. Clinical Infectious Diseases [serial online]. 2015;60(5):804-810.
18. Grohskopl LA, Chillag KL, Gvetadze R, et al. Randomized trial of clinical safety of daily oral tenofovir disoproxil fumarate among HIV-uninfected men who have sex with men in the United States. J Acquir Immune Defic Syndr. 2013;64(1):79-86.
19. Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. PLoS One 2011;6(8): e23688.
20. Van Damme L, Cornell A, Ahmed K, et al. Preexposure prophylaxis for HIV Infection among African women. The New England Journal of Medicine. 2012;367(5):411·22.
21. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women. The New England Journal of Medicine. 2015;372(6):509-518.
22. Cottrell ML, Yang KH, Prince HMA, et al. A Translational Pharmacology Approach to Predicting HIV Pre-Exposure Prophylaxis Outcomes in Men and Women Using Tenofovir Disoproxil Fumarate Emtricitabine. Journal of Infectious Diseases. 2016.
23. U.S. Food and Drug Administration Approves Expanded Indication for Truvada (Emtricitabine and Tenofovir Disoproxil Fumarate) for Reducing the Risk of Acquiring HIV-1 in Adolescents. Business Wire, 2018.
24. Hosek SG, Landovitz RJ, Kapogiannis B, et al. Safety and Feasibility of Antiretroviral Preexposure Prophylaxis for Adolescent Men Who Have Sex With Men Aged 15 to 17 Years in the United States. JAMA Pediatr. 2017 Nov 1;171(11):1063-1071.
25. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261·83.
26. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents: Department of Health and Human Services, 2013.
27. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection:2012 recommendations of the International Antiviral Society-USA panel. JAMA: The Journal of the American Medical Association. 2012;308(4):387-402.
28. Cohen MS, Chen YO, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. The New England Journal of Medicine. 2011;365(6):493·505.
29. Rodger A, Bruun T, Cambiano V, et al. HIV Transmission Risk Through Condomless Sex If HIV+ Partner On Suppressive ART: PARTNER Study. CROI. Boston, MA, 2014.
30. Gianelia S, Smith DM, Vargas MV, et al. Shedding of HIV and human herpesviruses in the semen of effectively treated HIV-1-infected men who have sex with men. Clin Infect Dis. 2013;57(3):441-7.
31. Panel on treatment of HIV·infected pregnant women and prevention of perinatal transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2012. http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf.