1. **What is PrEP?**

PrEP is short 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 high 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 and emtricitabine (TDF-FTC), which is available as a fixed-dose combination in a 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 a discussion about adherence, condom use, and other risk reduction methods.*

2. **What are the guidelines for prescribing PrEP?**

Comprehensive guidelines for prescribing PrEP have been published by the Centers for Disease Control and Prevention (CDC) in *A Clinical Practice Guideline*[^1], including a Clinical Providers’ Supplement.[^2]

*Both can be found on the CDC website: [www.cdc.gov/prescribeHIVprevention](http://www.cdc.gov/prescribeHIVprevention)*

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 questions arise or if prescribing advice is needed, clinicians should consult the National Clinicians Consultation Center PrEP Line @ 1-855-448-7737 (11:00 AM - 8:00 PM EST).

3. **Who can prescribe PrEP?**

Any licensed prescriber can prescribe TDF-FTC as PrEP. Specialization in infectious diseases 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.[^3]

4. **To whom should I offer PrEP?**

PrEP is for people without HIV who are at very high risk of acquisition from sex or injection drug use. People at high risk who should be assessed for PrEP include approximately:

- 1 in 4 sexually active gay and bisexual adult men without HIV
- 1 in 5 adults without HIV who inject drugs
- 1 in 200 sexually active heterosexual adults without HIV

Clinicians should also discuss PrEP with the following HIV-uninfected individuals (*other than those mentioned in the table on page 3*):

- Transgender individuals engaging in high-risk sexual behaviors
- Individuals who have been prescribed non-occupational post-exposure prophylaxis (PEP) and report continued high-risk behavior, or have used multiple courses of PEP
4. To whom should I offer PrEP? (continued)

Among men who have sex with men (MSM), high-risk behaviors can be quantified using the HIRI-MSM risk index featured in the national guidelines.\(^5\) (See section 6 of the CDC Clinical Providers' Supplement that accompanies the national guidelines.) This includes a screen for such behaviors as anal sex without a condom, having HIV-positive partners, and use of crystal meth or poppers.

Lastly, clinicians should consider the epidemiologic context of the sexual practices reported by the patient. The risk of HIV acquisition is determined by both the frequency of specific sexual practices (e.g., unprotected anal intercourse) and the likelihood that a sex partner has HIV infection. The same behaviors when reported as occurring in communities and demographic populations with high HIV prevalence or occurring with partners known to have HIV infection, are more likely to result in exposure to HIV and so will indicate greater need for intensive risk-reduction methods (PrEP, multisession behavioral counseling) than when they occur in a community or population with low HIV prevalence (see http://www.AIDS-vu.org or http://www.cdc.gov/nchhstp/atlas/).

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### Recommended Indications for PrEP

#### Men who have sex with men
- Adult or adolescent male weighing at least 35kg (77lbs)
- Without acute or established HIV infection
- Any male sex partners in past 6 months (if also has sex with women, see next box)
- Not in a monogamous partnership with a recently tested, HIV-negative man

AND at least one of the following
- Any anal sex without condoms (receptive or insertive) in past 6 months
- A bacterial STI (syphilis, gonorrhea, or chlamydia) diagnosed or reported in past 6 months

#### Heterosexual women and men
- Adult or adolescent person weighing at least 35kg (77lbs)
- Without acute or established HIV infection
- Any sex with opposite sex partners in past 6 months
- Not in a monogamous partnership with a recently tested HIV-negative partner

AND at least one of the following
- Is a man who has sex with both women and men (behaviorally bisexual) [also evaluate indications for PrEP use by previous box criteria]
- Infrequently uses condoms during sex with 1 or more partners of unknown HIV status who are known to be at substantial risk of HIV infection (PWID or bisexual male partner)
- Is in an ongoing sexual relationship with an HIV-positive partner
- A bacterial STI (syphilis, gonorrhea in women or men) diagnosed or reported in past 6 months

#### People who inject drugs
- Adult or adolescent person weighing at least 35kg (77lbs)
- Without acute or established HIV infection
- Any injection of drugs not prescribed by a clinician in past 6 months

AND at least one of the following
- Any sharing of injection or drug preparation equipment in past 6 months
- Risk of sexual acquisition (also evaluate by criteria in previous boxes)

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5. How is TDF-FTC for PrEP prescribed?

TDF-FTC for oral PrEP is taken once daily by mouth.\(^6\)*

**PrEP should be re-evaluated if:**

- The patient reports difficulty with adherence (efforts should be made to provide adherence counseling)
- The patient experiences toxicity or symptoms that cannot be managed
- The patient becomes pregnant

**Note:** In some cases, PrEP may continue for ongoing HIV prevention during pregnancy if the risk of ongoing HIV transmission is sufficiently high, i.e., woman is in an HIV-discordant partnership with uncertain viral suppression, and because pregnancy itself is associated with an increased risk of HIV acquisition. Condoms and supportive counseling, both for adherence and risk reduction, should be provided. Providers should discuss potential risks and benefits of beginning or continuing PrEP during pregnancy so that an informed decision can be made. (See Clinical Providers’ Supplement, Section 5: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-provider-supplement-2017.pdf)

*Full prescribing information is available at http://www.gilead.com/pdf/truvada_pi.pdf.*
6. **What is the evidence base for PrEP?**

Multiple studies have demonstrated that PrEP is effective. In all of these studies, HIV acquisition risk was lowest for **participants who took the pill consistently**. Specifically:

<table>
<thead>
<tr>
<th>Population</th>
<th>Effectiveness Estimate</th>
<th>Source</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men</td>
<td>92%</td>
<td>Grant[6], 2010</td>
<td>When taking PrEP with adherence indicated by laboratory-detected presence of drug, the risk of acquiring HIV is reduced by 92% for HIV-negative MSM. Missed doses result in lower effectiveness. Very high levels of adherence may increase effectiveness.</td>
</tr>
<tr>
<td>Heterosexual men and women</td>
<td>90%</td>
<td>Baeten[7], 2012</td>
<td>When taking PrEP with adherence indicated by laboratory-detected presence of drug, the risk of acquiring HIV is reduced by 90% for HIV-negative heterosexual men or women. Missed doses result in lower effectiveness. Very high levels of adherence may increase effectiveness.</td>
</tr>
<tr>
<td>Persons who inject drugs (PWIDs)</td>
<td>70%</td>
<td>Choopanya[8], 2013</td>
<td>When taking PrEP with adherence indicated by laboratory-detected presence of drug, the risk of acquiring HIV is reduced by 70% for HIV-negative PWIDs. Missed doses result in lower effectiveness. Very high levels of adherence may increase effectiveness.</td>
</tr>
</tbody>
</table>

Details of evidence for safety and efficacy of antiretroviral prophylaxis can be found in the Clinical Practice Guideline, pages 1-30. None of the studies found any significant safety concerns with use of daily oral PrEP. Some trial participants reported side effects, such as an upset stomach or loss of appetite, but these were mild and usually resolved in the first month.

**STRENGTHS AND LIMITATIONS OF EFFECTIVENESS ESTIMATES:**

- **The Grant, 2010 (iPrEx) study** was a randomized controlled trial evaluating daily PrEP use (TDF/FTC) against placebo among MSM. This effectiveness estimate comes from the case/control sub-analysis looking at new HIV infection associated with any drug detected, as measured by levels of emtricitabine (FTC) or tenofovir (TFV) in plasma or levels of FTC-TP or tenofovir diphosphate (TFV-DP) in peripheral blood mononuclear cells (PBMC).[6]

- **The Baeten, 2012 (Partners PrEP) study** was an RCT evaluating daily PrEP use (TDF/FTC) against placebo among heterosexual men and women. This effectiveness estimate comes from a case/control sub-analysis of new HIV infection associated with any drug detected, as measured by TFV plasma levels.[7]

- **The Choopanya, 2013 (Bangkok Tenofovir Study, BTS) study** was an RCT evaluating daily PrEP use (TDF) against placebo among PWID. This effectiveness estimate comes from a case/control sub-analysis of new HIV infections associated with any drug detected, as measured by TFV plasma levels.[8]

All effectiveness estimates are selected from subset analyses within the larger RCTs evaluating PrEP where PrEP use is defined as “any drug detected” and based on a biologic, objective measure for detecting the presence of drug. This is the only consistent objective measure of actual PrEP use across all populations at present. The estimates do not, however, reflect optimal adherence, which would likely yield even greater effectiveness.

7. **How important is adherence to PrEP?**

In all PrEP clinical trials to date, PrEP efficacy is dependent upon adherence.[9,10] According to a dedicated analysis of adherence from all trials to date, PrEP was non-efficacious when adherence was low, but when moderate or high adherence was achieved, efficacy was modest or relatively high, respectively.[10] Among the study subjects with detectable plasma tenofovir levels in iPrEx, Partners PrEP, TDF2, and BTS, efficacy ranged from 74% to 92%.[6,7,8,11,12]

Adherence to PrEP was also found to be highly associated with reduction of HIV risk in an open-label study (iPrEX OLE).[13] There were no HIV infections in participants using four or more tablets per week as detected by dried blood spot testing. Among participants with less drug detected, 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).[13]
8. **Is PrEP safe?**

Yes, in prevention studies to date, TDF-FTC for PrEP has not caused serious short- or medium-term safety concerns.[^6-15] Among HIV-infected adults, TDF-FTC has caused renal toxicity and decreased bone mineral density when used for treatment, and administered for months and years.[^5]

PrEP is considered safe for pregnant and breastfeeding women. Decisions about use during pregnancy must be individualized: available data suggest that TDF-FTC does not increase risk of birth defects.[^5]

PrEP is often used in pregnancy if the risk of ongoing HIV transmission is sufficiently high (such as in an HIV-discordant partnership with uncertain viral suppression) and because pregnancy itself is associated with an increased risk of HIV acquisition.

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.[^5]

9. **Who is not eligible for PrEP?**

1. **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 antiretrovirals to provide effective treatment.

2. **People with renal insufficiency.** Providers should confirm that the patient’s calculated creatinine clearance is $\geq 60$ 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).

10. **What baseline assessment is required for individuals beginning PrEP?**

**HIV Testing**

HIV testing is required to confirm that patients do not have HIV infection when they start taking PrEP medications. While antigen/antibody tests are preferred, at a minimum, clinicians should document a negative antibody test result within the week before initiating (or re-initiating) PrEP medications. The required HIV testing can be accomplished by (1) drawing blood (serum) and sending the specimen to a laboratory for a routine HIV EIA (enzyme-linked immunoassay) or (2) performing a rapid, point-of-care, FDA-approved, fingerstick blood test. Oral rapid tests should not be used to screen for HIV infection when considering PrEP use because they can be less sensitive than blood tests.[^16]

A listing of FDA-approved HIV tests, specimen requirements, and time to detection of HIV infection are available online at: [www.cdc.gov/hiv/testing/laboratorytests.html](http://www.cdc.gov/hiv/testing/laboratorytests.html)

Since PrEP is indicated for individuals who report injection or sexual behaviors that place them at substantial risk of HIV acquisition, clinicians should suspect acute HIV infection in persons known to have been exposed recently (e.g., a condom broke during sex with an HIV-infected partner, reported injection drug use with shared injection equipment). Therefore, clinicians should solicit a history of nonspecific signs or symptoms (continued)
**HIV Testing** (continued)

of viral infection during the preceding month or on the day of evaluation in all PrEP candidates with a negative or an indeterminate result on an HIV antibody test.

*For patients with signs/symptoms of acute HIV infection within the prior four weeks, the following options are suggested:*

1. Send blood for HIV antibody/antigen assay
   If the patient is negative, PrEP can be initiated. *(Preferred)*

2. Retest antibody in one month; defer PrEP decision.

3. Send blood for HIV-1 viral load (VL) assay. If the patient has VL<3,000 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, PrEP can be initiated.

**Renal Function**

In addition to confirming that any person starting PrEP medication is not infected with HIV, a clinician should determine renal function. TDF is widely used in combination antiretroviral regimens for the treatment of HIV infection.[17] Among HIV-infected persons prescribed TDF-containing regimens, decreases in renal function (as measured by estimated creatinine clearance \(eCrCl\)) have been documented, and occasional cases of acute renal failure, including Fanconi’s syndrome, have occurred.[18,19,20]

In the PrEP trials among otherwise healthy, HIV-uninfected adults, an eCrCl of ≥60 mL/min was an eligibility criterion. Safety data for TDF/FTC prescribed as PrEP to persons with reduced renal function are not available. There was a minimal, clinically insignificant decline in mean eCrCl among participants followed on PrEP for up to 5 years, with a return to baseline levels within weeks when PrEP medication was stopped. [21,22,23] Therefore, for all persons considered for PrEP, a serum creatinine test should be done, and an eCrCL should be calculated by using the Cockcroft-Gault formula. Any person with an eCrCl of <60 mL/min should not be prescribed PrEP with TDF/FTC.

**Hepatitis Serology**

Sexually active adults (especially MSM), and persons who inject illicit drugs, are at risk of acquiring HBV infection.[24] Vaccination against Hepatitis B virus (HBV) is recommended for all adolescents and adults, especially for MSM. Therefore, HBV infection status should be documented by screening serology before TDF/FTC is prescribed as PrEP. Those patients determined to be susceptible to HBV infection should be vaccinated.

HBV infection is not a contraindication to PrEP. Both TDF and FTC are active against HBV.[26] HBV-monoinfected patients taking TDF or FTC, whether as PrEP or to treat HBV infection, who then stop these medications must have their liver function closely monitored for reactivation of HBV replication that can result in hepatic damage.[5]

HCV serology is not required to be documented before TDF/FTC is prescribed. However, HCV serology is indicated for MSM, people who inject drugs, [25] and individuals born between 1945 and 1965 to identify those who may need treatment for HCV, which TDF/FTC does not treat.
HIV Status Algorithm

Figure 1

HIV immunoassay blood test
(rapid test if available)

Negative

Indeterminate

Positive

Link to care and treatment

Consider HIV + (pending confirmatory testing)

Signs/symptoms of acute HIV infection anytime in prior 4 weeks

No

Yes

Option 1

Retest antibody in one month, Defer PrEP decision

Option 2 (PREFERRED)

Send blood for HIV antibody/antigen assay*

Option 3

Send blood for HIV-1 viral load (VL) assay

HIV–

Eligible for PrEP

HIV+

Not Eligible for PrEP

HIV Status Unclear Defer PrEP decision

HIV+

Positive

VL>3,000 copies/mL

HIV+ Defer PrEP decision

HIV–

Negative

VL<3,000 copies/mL

HIV–

VL< level of detection no signs/symptoms on day of blood draw

Re-test in one month Defer PrEP decision

* Use only HIV antigen/antibody tests that are approved by FDA for diagnostic purposes
11. What additional support and ongoing assessments are required for patients on PrEP?

As mentioned previously, PrEP should be prescribed as part of a combination prevention plan. Studies of PrEP have involved substantial support, including regular HIV testing and discussions about adherence, safer sex behaviors, and condom use.

At minimum, while patients are on PrEP, CDC Guidelines recommend the following:

### Monitoring

<table>
<thead>
<tr>
<th>Prevention and medication support</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Assess adherence</td>
<td>At every visit</td>
</tr>
<tr>
<td>- Provide risk reduction counseling</td>
<td></td>
</tr>
<tr>
<td>- Offer condoms</td>
<td></td>
</tr>
<tr>
<td>- Manage side effects</td>
<td></td>
</tr>
</tbody>
</table>

### Laboratory testing

<table>
<thead>
<tr>
<th>HIV Testing (fingerstick or other blood test)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Every 3 months and</td>
<td></td>
</tr>
<tr>
<td>- Whenever there are symptoms of acute infection</td>
<td></td>
</tr>
</tbody>
</table>

**Sexually transmitted infection (STI) symptom screen and testing**

**FOR MALES:**
- Nucleic Acid Amplification Test (NAAT) to screen for gonorrhea and chlamydia, based on exposure site
- Test for syphilis

**FOR FEMALES:**
- Nucleic Acid Amplification Test (NAAT) to screen for gonorrhea, based on exposure site
- Test for syphilis

* Because chlamydia is very common, especially in young women, and does not strongly correlate with risk of HIV acquisition, regular screening for chlamydia is not recommended for all sexually active women as a component of PrEP care. However, clinicians should refer to the 2015 STD guidelines for recommendations about chlamydia testing frequency for women regardless of PrEP use.

<table>
<thead>
<tr>
<th>Symptom screen:</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>- At every visit</td>
<td></td>
</tr>
</tbody>
</table>

**Testing:**
- Every 3 months for sexually active persons with symptoms
- Every 3 months for asymptomatic MSM at high risk for recurrent STIs (e.g., those with recent STIs or multiple sex partners)
- Every 6 months for sexually active persons, even if asymptomatic
- Whenever symptoms are reported

<table>
<thead>
<tr>
<th>Serum creatinine and calculated creatinine clearance</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 3 months after initiation, then every 6 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pregnancy testing</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3 months</td>
<td></td>
</tr>
</tbody>
</table>

12. Will PrEP medication be covered by my patients’ health insurance?

Most insurance plans and state Medicaid programs are covering TDF-FTC as PrEP. Prior authorization may be required.

**Patient assistance program:** A commercial medication assistance program provides free PrEP medications to people with limited income and no insurance to cover PrEP care. The paperwork must be signed and submitted by a licensed clinical provider.

**Co-pay assistance program:** Income is not a factor in eligibility.

More information about both of these programs is available at: https://start.truvada.com/paying-for-truvada
13. How could a patient acquire HIV infection while taking PrEP?

Patients who are being prescribed PrEP may acquire HIV infection for several reasons. When it is detected at the first follow-up visit after PrEP initiation, it can indicate that the patient had undetected acute infection when PrEP was initiated. When infection is detected at later follow-up visits, as it most commonly occurs, it may be because patients have stopped taking PrEP, have been taking it infrequently, or have been stopping and restarting it without retesting for HIV infection before restarting. Rarely, despite high adherence to continuous daily dosing, patients taking PrEP have acquired HIV infection. This can occur because of exposure to a drug-resistant viral strain or simply because with daily use PrEP protection is high but not 100%.

In all cases, once additional laboratory tests have confirmed an initial positive HIV test from a PrEP patient’s follow-up visit, the following steps should be taken:

- Initiation of an HIV treatment regimen by adding medication to daily TDF/FTC
- Determination of CD4 lymphocyte count and viral load to guide therapeutic decisions
- Documentation of results of genotypic HIV viral resistance testing to guide future treatment decisions
- Provision of, or referral to, an experienced provider for the ongoing medical management of HIV infection
- Counseling about their HIV status and steps they should take to prevent HIV transmission to others and to improve their own health
- Assistance with, or referral to, the local health department for the identification of sex partners who may have been recently exposed to HIV so that they can be tested for HIV infection, considered for nonoccupational postexposure prophylaxis (nPEP), and counseled about their risk-reduction practices
- Reporting of new HIV infection to the local health department

14. If I take care of both members of an HIV-discordant couple, is it preferable to treat just the HIV-positive partner, just the HIV-negative partner, or both?

Experts recommend that all people with HIV be treated, regardless of clinical status or CD4 cell count.\[^{17,30}\] Virologic suppression of the HIV-infected partner protects his or her health and reduces the risk of HIV transmission to the HIV-uninfected partner.\[^{31}\]

Whether the HIV-negative partner should take PrEP if the positive partner is virologically undetectable varies by case. 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.

The need for PrEP to protect the negative partner is greatly reduced if the positive partner achieves and maintains an undetectable viral load. Recent large cohort studies suggest that the risk of seroconversion in mutually monogamous, HIV-discordant couples may be negligible.\[^{32}\]

PrEP can be indicated to protect the negative partner if the current viral load of the positive partner is not known, if the positive partner recently had an undetectable plasma viral load but has occasional lapsed adherence to antiretroviral therapy, or if a potential risk of STIs in the positive partner could cause genital tract viral load increases.\[^{33}\] PrEP may also be indicated for the negative partner in an HIV-discordant couple when he/she has additional (non-main) sexual partners.\[^{31}\]
REFERENCES


