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-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 adherence/risk behavior counseling, HIV prevention education and provision of condoms.

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2. What are the guidelines for prescribing PrEP?

CDC comprehensive guidelines for prescribing PrEP exist:

- Centers for Disease Control (CDC) Guidelines including a Clinical Providers' Supplement http://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf

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.

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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 and Men	Injection Drug Users
Signs of substantial HIV risk	• HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • Inconsistent or no condom use • Commercial sex work	• HIV-positive sexual partner • Recent bacterial STI • High number of sex partners • Inconsistent or no condom use • Commercial sex work • In high-prevalence area or network	• HIV-positive injecting • Sharing injection • Recent drug treatment (but currently injecting)

In addition, clinicians should discuss PrEP with the following populations:

- Male-to-female and female-to male transgender individuals engaging in high-risk sexual behaviors
- People who inject drugs and report any of the following behaviors:
  - Sharing injection equipment (including to inject hormones among transgender individuals)
  - Injecting one or more times per day, injecting cocaine or methamphetamine
  - Engaging in high-risk sexual behaviors
- Individuals who use stimulant drugs associated with high-risk behaviors, such as methamphetamine
- Individuals who have been prescribed non-occupational post-exposure prophylaxis (nPEP) and demonstrate continued high-risk behavior or have used multiple courses of nPE

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4. 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 [5].

5. How is TDF-FTC for PrEP prescribed?

TDF-FTC for oral PrEP is taken once daily by mouth. NYS Guidelines provide the most detailed recommendations about PrEP prescribing,

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 refill must be preceded by a negative HIV test)

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

PrEP should be discontinued immediately if: (1) the patient becomes HIV-infected, (2) the patient experiences toxicity or symptoms that cannot be managed or (3) the patient becomes pregnant. [Note that in some cases, PrEP may be restarted for ongoing HIV prevention during pregnancy if the risk of ongoing HIV transmission is sufficiently high (such as in a sero-discordant partnership) and because pregnancy itself is associated with an increased risk of HIV acquisition, as discussed in question 7, as well.] Condoms and supportive counseling, both for adherence and risk reduction, are required. (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:

Study	Population	N	Results
iPrEX [6] *Brazil, Ecuador, Peru, SI Africa, Thailand, UISIA*	MSM	2,499	44% efficacy FTC/TDF
Partners PrEP Study [7] *Kenya, Uganda*	Heterosexual couples	4,758	67% efficacy TDF 75% efficacy FTC/TDF
TDF2 Study [8] *Botswana*	Young men and women	1,200	62% efficacy FTC/TDF
Bangkok Tenofovir Study [11] *Thailand*	IDUs	2,400	49% efficacy TDF

In all PrEP clinical trials to date, PrEP efficacy appears to be dependent upon adherence [12,13]. 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 [13]. Among the study subjects with detectable plasma tenofovir levels in iPrEx, Partners PrEP, TDF2, and BTS, efficacy ranged from 74 to 92% [6,7,8,11].

Adherence to PrEP was also found to be highly associated with reduction of HIV risk in an open-label study (iPrEX OLE) [14]. There were no HIV infections in participants using four or more tablets per week as detected by dried blood spot. 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)

7. Is PrEP safe?

TDF-FTC has caused renal toxicity and decreased bone mineral density when used by HIV-infected people for HIV treatment and administered for months and years. However, in prevention studies to date, TDF-FTC for PrEP has not caused serious short-term safety concerns [5,15,16].

PrEP is considered safe for women of child-bearing age. Decisions about use during pregnancy must be individualized: while available data suggest that TDF-FTC does not increase risk of birth defects, there are not enough data to exclude the possibility of harm. (TDF-FTC: Pregnancy Class B.) PrEP is often used in pregnancy if the risk of ongoing HIV transmission is sufficiently high (such as in a sero-discordant partnership) 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.

8. Is PrEP safe?

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 ε60 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).

9. Does PrEP work in women?

Two trials of PrEP in women were stopped early for futility by their respective data safety and monitoring boards [9,10]. 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. Although one study's results have not yet been published, 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. Therefore, current recommendations include woman as candidates for PrEP.

10. 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.

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):

1. Retest antibody in one month; defer PrEP decision.
2. Send blood for HIV antibody/antigen assay (i.e., fourth generation HIV testing). If the patient is negative, it is acceptable to initiate PrEP.
3. 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 (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, treatment for active HBV must be continued.

11. 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 monthly HIV testing and intensive adherence and risk reduction counseling, as well as HIV prevention education and condom provision.

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

Monitoring	Frequency
Prevention and medication support	
Assess adherence	At every visit
Provide risk reduction counseling	
Offer condoms	
Manage side effects	
Laboratory testing	
HIV testing (CDC Guidelines: Any testing except oral rapid testing)	• Every 3 months and • Whenever there are symptoms of acute infection (serologic screening
Sexually transmitted infection (STI) symptom screen and testing • NAAT (nucleic acid amplification test) to screen for gonorrhea and chlamydia, based on exposure site • Rapid plasma reagin (RPR) • Inspection for anogenital lesions	Symptom screen: • At every visit Testing: • At least every 6 months, even if asymptomatic (Note: Monogamous sero-discordant couples may not need STI screening as
Hepatitis C Antibody Test	At least every 12 months for: • People who use drugs • MSM • People with multiple sexual partners
Serum creatinine and calculated creatinine clearance	At 3 months after initiation, then every 6 months
Urinalysis	Every 12 months
Pregnancy testing	Every 3 months

12. What additional support and ongoing assessment are required for patients on PrEP?

TDF-FTC as PrEP was added to the NH Medicaid formulary in January 2013. Prior authorization is required. Many other insurance plans cover PrEP.

The manufacturer of Truvada (Gilead) has established several programs to help cover the cost of PrEP. Providers can assist their patients by applying for assistance (either for help with the Truvada co-pay if the patient is insured or for complete coverage of the medication if the patient does not have insurance or needs financial assistance). The application form for Gilead's patient assistance programs is available at https://start.truvada.com/Content/pdf/Medication_Assistance_Program.pdf.

Patient assistance program: Those earning <500% of the federal poverty level ($58,350 for an individual living alone in 2014) are eligible. The cost of the medication and some additional screening tests are covered. The paperwork must be signed and submitted by a licensed clinical provider.

Co-pay assistance program: Income is not a factor in eligibility. Patients are reimbursed the amount of the co-pay up to $200 per month. The paperwork must be signed and submitted by a licensed clinical provider.

The retail cost of medications is approximately $1,300 to $1,400 per month. To determine prices at nearby pharmacies, check GoodRx at http://www.goodrx.com.

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

National experts recommend that **all** people with HIV be treated, regardless of clinical status or CD4 cell count [17, 18]. Virologic suppression of the HIV-infected partner protects his or her health and the health of the HIV-uninfected partner [19]. 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.

Factors against providing PrEP to the negative partner if the positive partner has an undetectable plasma viral load include recent large cohort studies suggesting that the risk of seroconverstion in stable, serodiscordant couples may be negligible [20].

Factors for providing PrEP to the negative partner if the positive partner has an undetectable plasma viral load include the fact 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 [21]. Additionally, many studies have supported that much HIV transmission is from non-main partners [19].

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