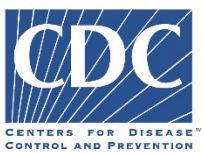
US PUBLIC HEALTH SERVICE

PREEXPOSURE PROPHYLAXIS FOR THE PREVENTION OF HIV INFECTION IN THE UNITED STATES –2017 UPDATE

CLINICAL PROVIDERS' SUPPLEMENT



What's New in the Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2017 Update – Clinical Providers' Supplement?

(Published Online March 2018)

The Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Providers' Supplement was published in an electronic format in July 2014 so that it could be updated as relevant changes in supporting evidence became available. The Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2016 Update – Clinical Providers' Supplement includes revisions to several sections. These revisions are highlighted throughout the document and are intended solely to update the developing evidence base and to clarify specific points in clinical care. No changes were made to the graded recommendations for the use of PrEP in the US.

New: Section 7 HIV Incidence Risk Index for Injection Drug Users

Added recently published validated risk screening tool

New: Section 8 Management of Patients Who Acquire HIV While On PrEP

Added additional detail about recommended steps in the clinical management at visits when seroconversion is detected in patients being prescribed PrEP

New: Section 9 Transition of Patients From nPEP to PrEP

Added additional detail about recommended steps in the clinical management of patients who are concluding a course of nPEP and transitioning directly to PrEP

Section 12 PrEP-related ICD, CPT, and LOINC Codes

Deleted ICD-9 codes since they no longer in use

Section 13 Potential PrEP Quality Practice Measures

Revised measure of medication prescription to measure medication adherence assessment

Section 14 Methods for Developing the PrEP Clinical Practice Guideline

Consolidated all information about the guidelines development and update process into this section and provided details about the systematic literature review methods.

Minor revisions were also made to correct typos, add references, and update content from cited guidelines and source materials.

Disclaimers:

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For more clinical advice about PrEP guidelines:

- call the National Clinicians Consultation Center PrEPline at **855-448-7737** or
- go to their website at http://nccc.ucsf.edu/clinician-consultation/prep-pre-exposure-prophylaxis/

Supplementary Materials:

Contents

Introduction

Recent findings from several clinical trials have demonstrated safety[1] and a substantial reduction in the rate of HIV acquisition for men who have sex with men (MSM)[2], men and women in heterosexual discordant couples[3], and heterosexual men and women recruited as individuals[4] who were prescribed daily oral antiretroviral preexposure prophylaxis (PrEP) with a fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). The demonstrated efficacy of PrEP was in addition to the effects of repeated condom provision, sexual risk-reduction counseling, and the diagnosis and treatment of sexually transmitted infection (STI) that were provided to all trial participants. In July 2012, after reviewing these trial results, the U.S. Food and Drug Administration (FDA) approved an indication for the use of Truvada® (TDF/FTC) "in combination with safer sex practices for pre-exposure prophylaxis (PrEP) to reduce the risk of sexually acquired HIV-1 in adults at high risk" [5,6]. In July 2013, an additional clinical trial found that daily oral TDF reduced the rate of HIV acquisition for persons who inject drugs (PWID) (also called injection drug users [IDU]) [7].

On the basis of these trial results and the FDA approval, the U.S. Public Health Service has published a comprehensive clinical practice guideline for the use of PrEP for the prevention of HIV infection in the United States and updated it in 2017. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

This supplement to the PHS PrEP Clinical Practice Guidelines is intended to provide additional information that may be useful to clinicians providing PrEP. As additional materials become available, this document will be updated.

Section 1	Contains a template checklist that clinicians can complete and share with patients to document the services provided to PrEP patients and the actions expected from patients to maximize the efficacy and safety of PrEP.
Sections 2-4	Contain templates for informational handouts that can be provided to patients
Section 5	Contains an information sheet for providers counseling patients about PrEP use during conception, pregnancy and breastfeeding.
Section 6	Contains the HIV incidence Risk Index for MSM, a tool that clinicians may use to quickly and systematically determine which men are at especially high risk for acquiring HIV infection, for whom PrEP may be indicated.
Section 7	Contains the HIV incidence Risk Index for PWID, a tool that clinicians may use to quickly determine which persons who inject drugs are at especially high risk for acquiring HIV infection, for whom PrEP may be indicated.
Section 8	Contains more detailed information about the clinical management of patients who acquire HIV infection while on PrEP.
Section 9	Contains more detailed information about the clinical management of transitioning patients from nPEP to PrEP.
Sections 10-11	Contain more detailed information than that included in the guidelines about methods and resources for counseling patients receiving PrEP about medication adherence and HIV risk reduction behaviors.

Sections 12	Contains information relevant to administrative and billing codes for PrEP related services.
Section 13	Contains potential practice quality practice measures.
Section 14	Documents the methods used to develop the PHS PrEP Clinical Practice Guidelines.

Section 1 Patient/Provider Checklist

Organization/Clinic Name

CHECKLIST FOR INITIATING PREEXPOSURE PROPHYLAXIS (PrEP)

_____ _____

Print name of provider Print name of patient

_____

Today's date (month/day/year)

Provider Section

I have provided this patient with the following: (check all as completed):

- ☐ Assessment for possible acute HIV infection
- ☐ Indicated laboratory screening to determine indications for these medications
- ☐ An HIV risk assessment to determine whether PrEP is indicated for this patient
- ☐ A medication fact sheet listing dosing instructions and side effects
- ☐ Counseling or a referral for counseling on condom use and any other HIV risk-reduction methods this patient may need
- ☐ Advice on methods to help the patient to take medication daily as prescribed
- ☐ Information about PrEP use during conception and pregnancy (when indicated)
- ☐ A prescription for Truvada (300 mg tenofovir disoproxil fumarate, 200 mg emtricitabine)
- ☐ A follow-up appointment date

As the provider, I will:

- Limit refill periods to recommended intervals for repeat HIV testing (at least every 3 months)
- Conduct follow-up visits at least every 3 months that include the following:
  - Assessment of HIV status (including signs or symptoms of acute HIV infection)
  - Assessment of side effects and advice on how to manage them
  - Assessment of medication adherence and counseling to support adherence
  - Assessment of STI symptoms, HIV risk behavior and counseling support for risk-reduction practices
- Inform the patient of any new information about PrEP and respond to questions

Patient Section

It has been explained to me that:

- Taking a dose of PrEP medication every day may lower my risk of getting HIV infection
- This medicine does not completely eliminate my risk of getting HIV infection, so I need to use condoms during sex
- This medicine may cause side effects so I should contact my provider for advice by calling _____ if I have any health problems
- It is important for my health to find out quickly if I get HIV infection while I'm taking this medication, so
    - I will contact my provider right away if I have symptoms of possible HIV infection (fever with sore throat, rash, headache, or swollen glands)
- My provider will test for HIV infection at least once every 3 months

Therefore, I will:

- Try my best to take the medication my provider has prescribed every day
- Talk to my provider about any problems I have in taking the medication every day
- Not share the medication with any other person
- Attend all my scheduled appointments
- Call _____ to reschedule any appointments I cannot attend

Give one copy to patient

Section 2 PrEP Information Sheet

Pre-exposure Prophylaxis (PrEP) for HIV Prevention

Frequently Asked Questions

What is PrEP?

"PrEP" stands for **pre**exposure **p**rophylaxis. The word "prophylaxis" (pronounced pro fil ak sis) means to prevent or control the spread of an infection or disease. The goal of PrEP is to prevent HIV infection from taking hold if you are exposed to the virus. This is done by taking a pill that contains 2 HIV medications every day. These are the same medicines used to stop the virus from growing in people who are already infected.

Why take PrEP?

The HIV epidemic in the United States is growing. About 50,000 people get infected with HIV each year. More of these infections are happening in some groups of people and some areas of the country than in others.

Is PrEP a vaccine?

No. PrEP medication does not work the same way as a vaccine. When you take a vaccine, it trains the body's immune system to fight off infection for years. You will need to take a pill every day by mouth for PrEP medications to protect you from infection. PrEP does not work after you stop taking it. The medication that was shown to be safe and to help block HIV infection is called "Truvada" (pronounced tru va duh). Truvada is a combination of 2 drugs (tenofovir and emtricitabine). These medicines work by blocking important pathways that the HIV virus uses to set up an infection. If you take Truvada as PrEP daily, the presence of the medication in your bloodstream can often stop the HIV virus from establishing itself and spreading in your body. If you do not take the Truvada pills every day, there may not be enough medicine in your blood stream to block the virus.

Should I consider taking PrEP?

PrEP is not for everyone. Doctors prescribe PrEP for some patients who have a very high risk of coming in contact with HIV by not using a condom when they have sex with a person who has HIV infection. You should consider PrEP if you are a man or woman who sometimes has sex without using a condom, especially if you have a sex partner who you know has HIV infection. You should also consider PrEP if you don't know whether your partner has HIV infection but you know that your partner is at risk (for example, your partner inject drugs or is having sex with other people in addition to you) or if you have recently been told by a health care provider that you had a sexually transmitted infection. If your partner has HIV infection, PrEP may be an option to help protect you from getting HIV infection while you try to get pregnant, during pregnancy, or while breastfeeding.

How well does PrEP work?

PrEP was tested in several large studies with men who have sex with men, men who have sex with women, and women who have sex with men. All people in these studies (1) were tested at the beginning of the trial to be sure that they did not have HIV infection, (2) agreed to take an oral PrEP tablet daily,

(3) received intensive counseling on safer-sex behavior, (4) were tested regularly for sexually transmitted infections, and (5) were given a regular supply of condoms.

Several studies showed that PrEP reduced the risk of getting HIV infection.

- Men who have sex with men who were given PrEP medication to take, were 44% less likely to get HIV infection than were those men who took a pill without any PrEP medicine in it (a placebo). Forty-four percent was an average that included men who didn't take the medicine every day and those who did. Among the men who said they took most of their daily doses, PrEP reduced the risk of HIV infection by 73% or more, up to 92% for some.
- Among men and women in couples in which one partner had HIV infection and the other partner initially did not ("HIV-discordant" couples), those who received PrEP medication were 75% less likely to become infected than those who took a pill without any medicine in it (a placebo). Among those who said they took most of their daily doses, PrEP reduced the risk of HIV infection by up to 90%.
- In one study of men and women who entered the study as individuals (not as a couple), PrEP worked for both men and women in one study: those who received the medication were 62% less likely to get HIV infection; those who said they took most of their daily doses, were 85% less likely to get HIV infection. But in another study, only about 1 in 4 women (<26%) had PrEP medication found in their blood when it was checked. This indicated that few women were actually taking their medication and that study found no protection against HIV infection.

More information on the details of these studies can be found at http://www.cdc.gov/hiv/prep.

Is PrEP safe?

The clinical trials also provided safety information on PrEP. Some people in the trials had early side effects such as an upset stomach or loss of appetite but these were mild and usually went away within the first month. Some people also had a mild headache. No serious side effects were observed. You should tell your doctor if these or other symptoms become severe or do not go away.

How can I start PrEP?

If you think you may be at high risk for HIV, talk to your doctor about PrEP. If you and your doctor agree that PrEP might reduce your risk of getting HIV infection, you will need to come in for a general health physical, blood tests for HIV, and tests for other infections that you can get from sex partners. Your blood will also be tested to see if your kidneys and liver are functioning well. If these tests show that PrEP medicines are likely to be safe for you to take and that you might benefit from PrEP, your doctor may give you a prescription after discussing it with you.

Taking PrEP medicines will require you to follow-up regularly with your doctor. You will receive counseling on sexual behaviors and blood tests for HIV infection and to see if your body is reacting well to Truvada. You should take your medicine every day as prescribed, and your doctor will advise you about ways to help you take it regularly so that it stands the best chance to help you avoid HIV infection. Tell your doctor if you are having trouble remembering to take your medicine or if you want to stop PrEP.

If I take PrEP can I stop using condoms when I have sex?

You should not stop using condoms because you are taking PrEP. If PrEP is taken daily, it offers a lot of protection against HIV infection, but not 100%. Condoms also offer a lot of protection against HIV infection if they are used correctly every time you have sex, but not 100%. PrEP medications don't give you any protection from other infections you can get during sex, but condoms do. So you will get the most protection from HIV and other sexual infections if you consistently take PrEP medication and consistently use condoms during sex.

How long do I need to take PrEP?

You should discuss this with your doctor. There are several reasons that people stop taking PrEP. If your risk of getting HIV infections becomes low because of changes that occur in your life, you may want to stop taking PrEP. If you find you don't want to take a pill every day or often forget to take your pills, other ways of protecting yourself from HIV infection may work better for you. If you have side effects from the medication that are interfering with your life or if blood tests show that your body is reacting to PrEP in unsafe ways, your doctor may stop prescribing PrEP for you.

Section 3 Truvada Medication Information Sheet

Truvada Medication Information Sheet for Patients

Brand name: Truvada (tru va duh)

Generic name: tenofovir disoproxil fumarate and emtricitabine

Why is this medication prescribed?

- Truvada is one of several medications that are currently used to treat human immunodeficiency virus (HIV) and hepatitis B virus infection.
- Truvada is now being used to *prevent* HIV infection.
- Truvada is sometimes prescribed to some people who do not have HIV infection (for example, those who do not always use condoms or who have a sex partner that has HIV infection) to help reduce their chances of getting HIV infection
- When you take Truvada to prevent HIV infection, doctors refer to this use as "pre-exposure prophylaxis" or "PrEP".

How does Truvada (PrEP) help prevent HIV infection?

- HIV is a virus that attacks your body's immune cells (the cells that work to fight infections).
- The 2 medications that make up Truvada (tenofovir and emtricitabine) block important pathways that viruses use to set up infection.
- If you take Truvada as PrEP daily, the presence of the medication in your bloodstream can sometimes stop the virus from establishing itself and slow the spread of HIV in your body.
- By itself, PrEP with Truvada does not work all the time so you should also use condoms during sex for the most protection from HIV infection.

How should this medicine be used?

- You must take one tablet of Truvada by mouth every day.
- Follow the directions on your prescription label carefully, and ask your doctor or pharmacist to explain any part you do not understand.
- Do not stop taking Truvada without talking to your doctor. When your supply of Truvada starts to run low, contact your doctor or pharmacist to get more.
- You may be at higher risk of becoming infected with HIV if you miss doses or stop taking Truvada than if you take it every day.

What special precautions should I follow?

Before taking Truvada (tenofovir and emtricitabine) you must do the following:

- Tell your doctor and pharmacist if you are allergic to tenofovir, emtricitabine, or any other medications.
- Tell your doctor and pharmacist about all prescription and nonprescription medications, (vitamins, nutritional supplements, and herbal products) you are taking. Your doctor may need to change the doses of your medications or monitor you carefully for side effects.
- Tell your doctor if you have or have ever had kidney or liver disease.
- Tell your doctor if you become pregnant or if you are breastfeeding.

What special dietary instructions should I follow?

- Continue your normal diet unless your doctor tells you otherwise.

What should I do if I forget a dose?

- Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule.
- Do not take a double dose to make up for a missed one.

What side effects can this medication cause?

You may experience the following side effects while taking Truvada:

- upset stomach
- headache
- vomiting
- loss of appetite

These side effects usually fade during the first month of taking Truvada for PrEP. Tell your doctor if any of these symptoms are severe or do not go away.

Truvada may cause other side effects. Some side effects can be serious. Call your doctor immediately if you have any unusual problems while taking this medication or if you have any of the following:

- fever or chills especially with
- sore throat, cough, rash or other signs of infection

If you experience a serious side effect, you or your doctor may send a report to the Food and Drug Administration's (FDA) MedWatch Adverse Event Reporting program online (at http://www.fda.gov/Safety/MedWatch) or by phone (1-800-332-1088).

How should I store Truvada in my home?

- You should keep Truvada in the container it came in, tightly closed, and out of reach of children.
- You must store it at room temperature and away from excessive heat and moisture.
- Throw away any medication that is outdated or no longer needed. Talk to your pharmacist about the proper disposal of your medication.

What should I do in case of emergency/overdose?

- In case of overdose, call your local poison control center at 1-800-222-1222. If the person has collapsed or is not breathing, call local emergency services at 911.

What other information should I know?

- Do not let anyone else take your medication.
- Ask your pharmacist if you have any questions about refilling your prescription.
- Write a list of all of your prescription and over-the-counter medicines, as well as any vitamins, minerals, or other dietary supplements that you take.
- Bring your medication list with you each time you visit a doctor or if you are admitted to a hospital. Keep it with you always in case of emergencies.

Section 4 Patient Information Sheet – Acute HIV Infection

Information about Acute HIV Infection and PrEP

What is acute HIV Infection?

HIV stands for human immunodeficiency virus. This is the virus that causes AIDS.

Acute HIV infection is a name for the earliest stage of HIV infection, when you first get infected with the HIV virus. It is sometimes also called primary HIV infection. Many people with acute HIV infection have the following:

- A fever
- A tired feeling
- Swollen lymph nodes (also called lymph glands)
- Swollen tonsils (also called tonsillitis)
- A sore throat
- Joint and muscle aches
- Diarrhea
- A rash

These signs and symptoms of acute HIV infection can begin a few days after you are exposed to HIV and usually last for about 14 days. They could last for just a few days, or they could last for several months.

You might not realize your illness is acute HIV infection. For one thing, you may not have known that the person you had sex with had HIV infection. And the signs and symptoms of HIV infection may feel just like other common virus infections like flu, a cold, sore throat, or mononucleosis (mono).

What tests can show that I have acute HIV infection?

When HIV enters your body, it moves inside white blood cells called CD4 lymphocytes. HIV takes over the CD4 cells and makes billions of copies of the virus each day. The virus spread through your body.

Your body tries to defend itself against HIV by making antibodies (these antibodies try to block the virus from spreading in your body). Most HIV tests check to see if antibodies against HIV are in your blood. But it takes a few weeks before your body makes enough antibodies for the usual HIV tests to see them.

However, when you have acute HIV infection, you have a high amount of the HIV virus in your blood. Special tests can measure the amount of HIV in your blood. At the time you have acute HIV infection, you probably won't have enough HIV antibodies in your blood to measure, but you will have enough virus to measure. So if the blood tests do not find any antibody but do see the virus, your doctor will know that you're feeling sick because you have acute HIV infection.

How does it help to find out I have HIV at an early stage?

First, PrEP is used to help lower your chances of getting HIV infection. If you already have acute HIV infection you should not take PrEP.

Second, while PrEP helps protect people, especially when they take their doses every day, it is still possible to get HIV infection. So if you are taking PrEP and have the signs and symptoms mentioned above, it is important to see your doctor to be checked. If you have some other infection, like the flu, you should continue your PrEP medicines but if it is discovered that you have acute HIV infection, you should stop taking PrEP as soon as your tests show that you have HIV infection

Third, people who take PrEP for more than a couple of weeks while they have HIV infection can easily develop virus that can't be treated with those same drugs (resistant virus). So finding out quickly that you have HIV infection and stopping PrEP can protect your long term health and keep your treatment options open.

And fourth, when people have lots of virus in their body during acute HIV infection, they are more likely to pass the virus on to people they have sex with, especially since they may not know yet that they have gotten infected. For example, if your last HIV test result was negative and your partner also had a recent negative HIV test result, you might choose to have sex without a condom just at the time when it's very likely you would pass the virus on. So the sooner you know you have become infected, the more careful you can be to protect others from getting HIV infection.

How is HIV treated?

People who have HIV infection are treated with combinations of 3 or more medicines that fight HIV. Some doctors start people on treatment medications as soon as they become infected; other doctors wait for a while because the greatest benefits to a person's health are seen after they have been infected a while. Early treatment also reduces the chances that a person with HIV infection will pass the virus on to their sex partners.

What do I do if I suspect I might have acute HIV infection?

First, contact your doctor's office and arrange to be examined and have the right blood tests.

Second, discuss with your doctor whether to stop your PrEP medications or continue them until your test results are back.

Third, be especially careful to use condoms and take other safer sex measures to protect your partner(s).

Section 5 Provider Information Sheet – PrEP during Conception, Pregnancy, and Breastfeeding

Information for Clinicians
Counseling Patients about PrEP Use During Conception, Pregnancy, and Breastfeeding

PrEP use may be one of several options to help protect the HIV-negative male or female partner in a heterosexual HIV-discordant couple during attempts to conceive[8-10]. Pregnancy care providers may not have access to the medical records of the partner with HIV infection to document their viral load status. The extent to which PrEP use further decreases risk of HIV acquisition when the partner with HIV infection has a documented current undetectable viral load is unknown.

Based on

DHHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission[9]

Panel's Recommendations on Reproductive Options for HIV-Concordant and Serodiscordant Couples

For Couples who Want to Conceive

For Concordant (Both Partners are HIV-Infected) and Discordant Couples:

- Expert consultation is recommended so that approaches can be tailored to couples specific needs **(AIII)**.
- Partners should be screened and treated for genital tract infections before attempting to conceive **(AII)**.
- The HIV-infected partner(s) should attain maximum viral suppression before attempting conception **(AIII)**.

For Discordant Couples:

- The HIV-infected partner should be receiving combination antiretroviral therapy and demonstrate sustained suppression of plasma viral load below the limits of detection (AI).
- Administration of antiretroviral pre-exposure prophylaxis (PrEP) for 30 days before attempting conception and for 30 days after conception is achieved for HIV-uninfected partners may offer an additional tool to reduce the risk of sexual transmission, particularly if the HIV-infected partner's plasma viral load is unknown or detectable **(CIII)**. It is not known whether PrEP for the uninfected partner confers additional benefit when the infected partner receiving antiretroviral therapy has documented sustained viral suppression.

Discordant Couples with HIV-Infected Women:

- The safest conception option is assisted insemination, at home or in a clinician's office with a partner's sperm during the peri-ovulatory period **(AIII)**.

Discordant Couples with HIV-Infected Men:

- The use of donor sperm from an HIV-uninfected man with artificial insemination is the safest option **(AIII).**
- When the use of donor sperm is unacceptable, the use of sperm preparation techniques coupled with either intrauterine insemination or *in vitro* fertilization should be considered **(BII)**.

Based on

DHHS Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission[9]

Panel's Recommendations on Reproductive Options for HIV-Concordant and Serodiscordant Couples
• Semen analysis is recommended for HIV-infected men before conception is attempted to prevent unnecessary exposure to infectious genital fluid. Semen abnormalities appear to be more common among HIV-infected men than HIV-uninfected men (**AIII**).
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*

The following information is provided to help you inform your patients of current information about potential risks and benefits of PrEP use so that you and your patients can make an informed decision.

Key Points

- Provide education about PrEP and other methods of conception that minimize the risk of HIV transmission to both members of an HIV-discordant couple whenever possible.
- During counseling, include discussion of what is currently known and unknown about
  - Potential benefits
  - Potential risks
- If you prescribe PrEP, include the following in counseling:
  - Importance of adherence to daily doses of medication
  - Importance of continuing condom use after conception to protect against sexually transmitted infections and to add protection against HIV infection
- Signs and symptoms of acute HIV infection and the need for urgent HIV testing if HIV infection is suspected

FOR AN HIV-NEGATIVE MAN PLANNING PREGNANCY WITH AN HIV-POSITIVE FEMALE PARTNER

Options

Reducing the risk of HIV acquisition by an HIV-negative man during conception can be achieved by use of the following, singly or ideally in combination[10-13]:

- Antiretroviral treatment of the HIV-positive female partner to achieve an undetectable viral load[13]
- STI diagnosis and any indicated treatment for both partners before conception attempts
- Daily, oral doses of TDF/FTC beginning 1 month before a conception attempt and continuing for 1 month after a conception attempt. PrEP may be indicated when the partners recent viral load is unknown, reported to be detectable, or cannot be documented as undetectable[14].

AND EITHER

- Limit sex without a condom (natural conception) to peak fertility times identified by home or laboratory tests for ovulation[15.]

OR

- Intravaginal insemination[13] (either at home or in the clinic) with a fresh semen sample

Potential Benefits of PrEP use

In clinical trials with heterosexually active adults, daily oral PrEP with TDF/FTC was safe and reduced the risk of HIV acquisition by an average of 63%-75%. Higher levels of protection (≥90%) were found among persons whose drug levels in their blood indicated that they had consistently taken the medication[3,4].

Potential Risks of PrEP use

In PrEP trials, follow-up with persons taking medication has been conducted for an average of 1-4 years. Although no serious health risks were associated with PrEP use by HIV-uninfected adults, the long-term safety of PrEP has not yet been determined.

FOR AN HIV-NEGATIVE WOMAN PLANNING PREGNANCY WITH AN HIV-POSITIVE MALE PARTNER

Options

Reducing the risk of HIV acquisition by an HIV-negative woman during conception can be achieved by use of the following, singly or ideally in combination[10,13]:

- Antiretroviral treatment of the HIV-positive male partner to achieve an undetectable viral load[13]
- STI diagnosis and any indicated treatment for both partners before conception attempts
- Daily, oral doses of TDF/FTC beginning 1 month before a conception attempt and continuing for 1 month after a conception attempt. PrEP may be indicated when the partners recent viral load is unknown, reported to be detectable, or cannot be documented as undetectable[14].

AND EITHER

- Limit sex without a condom (natural conception) to peak fertility times identified by home or laboratory tests for ovulation in the female partner[15].

OR

- Intravaginal[16] or intrauterine insemination, or intracytoplasmic sperm injection with a semen sample processed by "sperm washing" and confirmed to have a negative test result for the presence of remnant HIV[16-17]. This option may be indicated for couples with fertility problems.

Potential Benefits of PrEP use

In clinical trials with heterosexually active adults, daily oral PrEP with TDF/FTC was safe and reduced the risk of HIV acquisition by an average of 63%-75%. Higher levels of protection (≥90%) were found among persons whose drug levels in their blood indicated that they had consistently taken the medication[3,4].

The risk of HIV acquisition increases during pregnancy[19], as does the risk of HIV transmission to an infant born to a mother who becomes infected during pregnancy or breastfeeding[20] Therefore, an HIV-negative woman whose sexual partner/spouse has HIV infection may benefit from continuing PrEP use throughout her pregnancy and breastfeeding to protect herself and her infant[a]

Potential Risks of PrEP use

In PrEP trials, follow-up with persons taking medication has been conducted for an average of 1-4 years. Although no serious health risks were associated with PrEP use by HIV-uninfected adults, the long-term safety of PrEP has not yet been determined.

In PrEP trials women were taken off medication as soon as pregnancy was detected. During these trials, no health problems have been associated with PrEP use by women in early pregnancy or for their offspring. However, the long-term safety of PrEP taken by HIV-uninfected women after fetal (during pregnancy) or infant (during breastfeeding) exposure is not yet determined.

No adverse effects have been found among infants exposed to TDF/FTC when the medications were taken as part of a treatment regimen for HIV-infected women during pregnancy[21-23] or during breastfeeding (for which data suggest limited drug exposure [24-27]).

If you prescribe PrEP to a woman while pregnant, you are encouraged to prospectively and anonymously submit information about the pregnancy to the Antiretroviral Use in Pregnancy Registry (http://www.apregistry.com/).

[a] Although the DHHS Perinatal HIV Guidelines state that "pregnancy and breastfeeding are not contraindications for PrEP"[9], the FDA-approved package insert[6] says, "If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy" and "mothers should be instructed not to breastfeed if they are receiving TRUVADA, whether they are taking TRUVADA for treatment or to reduce the risk of acquiring HIV-1.". Therefore both are currently off-label uses of Truvada.

References

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Section 6 MSM Risk Index

Epidemiologic studies have identified a wide range or personal, relationship, partner, social, cultural, network, and community factors that may be associated with the presence of HIV infection. However, to provide PrEP (or other intensive HIV prevention services), it is necessary to briefly and systematically screen for key information about those factors that are predictive of very high risk of acquiring HIV infection.

This section contains a tool that clinicians may use to quickly and systematically determine which MSM are at especially high risk of acquiring HIV infection, and for whom PrEP may be indicated.

	MSM Risk Index [28]		
1	How old are you today?	If <18 years, score 0 If 18-28 years, score 8 If 29-40 years, score 5 If 41-48 years, score 2 If 49 years or more, score 0	_____
2	In the last 6 months, how many men have you had sex with?	If >10 male partners, score 7 If 6-10 male partners, score 4 If 0-5 male partners, score 0	_____
3	In the last 6 months, how many times did you have receptive anal sex (you were the bottom) with a man when he did not use a condom?	If 1 or more times, score 10 If 0 times, score 0	_____
4	In the last 6 months, how many of your male sex partners were HIV-positive?	If >1 positive partner, score 8 If 1 positive partner, score 4 If <1 positive partner, score 0	_____
5	In the last 6 months, how many times did you have insertive anal sex (you were the top) with a man who was HIV- positive when you did not use a condom?	If 5 or more times, score 6 If 0-4 times, score 0	_____
6	In the last 6 months, have you used methamphetamines such as crystal or speed?	If yes, score 6 If no, score 0	_____
		Add down entries in right column to calculate total score	_____ TOTAL SCORE*

* If score is 10 or greater, evaluate for intensive HIV prevention services including PrEP.
If score is below 10, provide indicated standard HIV prevention services.

Section 7 PWID (IDU) Risk Index

Epidemiologic studies have identified a wide range or personal, relationship, partner, social, cultural, network, and community factors that may be associated with the presence of HIV infection. However, to provide PrEP (or other intensive HIV prevention services), it is necessary to briefly and systematically screen for key information about those factors that are predictive of very high risk of acquiring HIV infection.

This section contains a tool that clinicians can use to quickly and systematically determine which persons who inject drugs (PWID) (also called injection drug users [IDU]) are at especially high risk for acquiring HIV infection, and for whom PrEP may be indicated.

PWID (IDU) Risk Index [29]				
1	How old are you today (in years)?	If <30 years, score 38 If 30- 39 years, score 24 If 40-49 years, score 7 If ≥50 years, score 0		_____
2	In the last 6 months, were you in a methadone maintenance program?	If yes, score 0 If no, score 31		_____
3	In the last 6 months, how often did you inject heroin?	If 1 or more times, If 0 times,	Injection sub-score 1 Injection sub-score 0	_____
	In the last 6 months, how often did you inject cocaine?	If 1 or more times, If 0 times,	Injection sub-score 1 Injection sub-score 0	_____
	In the last 6 months, how often did you share a cooker?	If 1 or more times, If 0 times,	Injection sub-score 1 Injection sub-score 0	_____
	In the last 6 months, how often did you share needles?	If 1 or more times, If 0 times,	Injection sub-score 1 Injection sub-score 0	_____
	In the last 6 months, how often did you visit a shooting gallery?	If 1 or more times, If 0 times,	Injection sub-score 1 Injection sub-score 0	_____
Add the five injection subscores to obtain a Composite Injection Subscore		If sum of five injection subscores is; then Composite Injection Score is: 0 0 1 7 2 21 3 24 4 24 5 31		_____
Add the scores for age and methadone use to the Composite Injection Subscore to yield a Total Score				_____ Total Score*

* If the total score is 46 or greater, evaluate for PrEP or other intensive HIV prevention services for PWID. If score is 45 or less, provide indicated standard HIV prevention services for PWID. To identify active PWID in a clinician's practice, we recommend asking all their patients a routine question: "Have you ever injected drugs that were not prescribed for you by a physician?" If yes, ask, "When was the last time you injected any drugs?" Only complete PWID risk index if they have injected any nonprescription drug during the past 6 months.

Section 8 Management of Patients Who Acquire HIV While on PrEP

Patients who are being prescribed PrEP might acquire HIV infection for several reasons. When HIV infection 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 might 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[30] or simply because, even with daily use, PrEP protection is high but not 100%[31].

In all cases, when an HIV test during a follow-up visit indicates possible infection in a PrEP patient, the following steps should be taken:

- Counsel the patient about their HIV status and the resulting management plan:
    - If a single rapid antibody blood test was positive, explain the need to confirm presumptive HIV-positive status with laboratory testing.
    - If a rapid 4th generation (antigen/antibody) blood test was positive, explain high likelihood of HIV infection that will need to be confirmed with additional laboratory testing.
    - If a positive HIV test was based on laboratory testing with confirmatory results already known, explain certainty of HIV diagnosis.
    - Ask about signs and symptoms of acute infection since last clinic visit as well as PrEP medication adherence history.
- Conduct confirmatory HIV testing (if not completed already) and supplemental tests, if indicated:
    - If one or more rapid tests were positive, draw blood for confirmatory laboratory-based HIV testing with adequate blood for reflex HIV viral load testing if confirmed to be HIV infected.
    - If laboratory-based testing was positive, draw blood for HIV viral load, CD4 cell count, and HIV resistance testing.
    - For persons with confirmed HIV infection, conduct the following supplemental testing indicated for initiation of HIV treatment, including but not necessarily limited to the following[32]:
        - Chemistry screen, ALT, AST, bilirubin, CBC with differential, urinalysis, and pregnancy test (if female).
        - Fasting lipid profile, glucose, and hemoglobin A1c are also indicated, on the day that seroconversion is detected, if possible.
- Convert the PrEP regimen to an HIV treatment regimen recommended by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents[32].
    - It is not necessary to stop antiretrovirals entirely while waiting for additional laboratory test results. In the most likely event that the patient has HIV infection, immediate initiation of HIV treatment is indicated. The following regimens are recommended as of July 14, 2016 but the treatment guidelines should be consulted for updates[32]:
    - Continue the prescription of Truvada (TDF 300 mg/FTC 200 mg) once daily pending results of resistance tests
    - Add either:

- Dolutegravir (Tivicay) 50 mg once daily

  OR

- Darunavir (Prezista) 800 mg with Ritonavir (Norvir) 100 mg once daily.

In cases where a viral strain with significant resistance to tenofovir is later identified, the regimen can then be optimized. In cases where HIV infection is not confirmed, return to the PrEP regimen can be accomplished by dropping the additional treatment medication.

- Provide client education about time to viral load suppression:
  - Reinforce the importance of medication adherence for the patient's long-term health.
  - Discuss the importance of condom use to protect sexual partners and provide condoms.
  - Offer HIV testing for sex and drug injection partners and assistance with disclosure, if desired.
  - Ask if the patient had condomless sex or shared injection equipment during the past 72 hours, and if yes, offer nPEP for exposed partners.

- Consult with and transfer care to an experienced HIV care provider, if necessary.
  - Clinicians can call the National Clinical Consultation Center toll-free at (800) 933-3413.

- Discuss or complete insurance paperwork necessary for coverage of treatment medication.
  - Patients who are receiving medication through PrEP-specific medication assistance programs will need to switch to an HIV treatment assistance program.
  - Public or private insurance plans will generally not require additional paperwork but prior authorizations for PrEP may raise questions when switching to a prescription for a treatment regimen.

- Schedule follow-up visits (including social services, if required).

- Complete an HIV case report for the health department (completion of fields related to PrEP use at the time of seroconversion are highlighted in red below).

HIV Antiretroviral Use History (record all dates as mm/dd/yyyy)

Main source of antiretroviral (ARV) use information (select one)
_ Patient Interview _ Medical Record Review _ Provider Report _ NHM&E _ Other

Date patient reported information __ __ / __ __ / __ __ __ __

Ever taken any ARVs? _ Yes _ No _ Unknown

If yes, reason for ARV use (select all that apply)

_ HIV Tx	ARV medications		Date began __ __ / __ __ / __ __ __ __	Date of last use __ __ / __ __ / __ __ __ __
_ PrEP	ARV medications	Truvada	Date began __ __ / __ __ / __ __ __ __	Date of last use __ __ / __ __ / __ __ __ __
_ PEP	ARV medications		Date began __ __ / __ __ / __ __ __ __	Date of last use __ __ / __ __ / __ __ __ __
_ PMTCT	ARV medications		Date began __ __ / __ __ / __ __ __ __	Date of last use __ __ / __ __ / __ __ __ __
_ HBV Tx	ARV medications		Date began __ __ / __ __ / __ __ __ __	Date of last use __ __ / __ __ / __ __ __ __
_ Other				
	ARV medications		Date began __ __ / __ __ / __ __ __ __	Date of last use __ __ / __ __ / __ __ __ __

HIV Testing History (record all dates as mm/dd/yyyy)

Main source of testing history information (select one)
_ Patient Interview _ Medical Record Review _ Provider Report _ NHM&E _ Other

Date patient reported information __ __ / __ __ / __ __ __ __

Ever had previous positive HIV test? _ Yes _ No _ Unknown

Date of first positive HIV test __ __ / __ __ / __ __ __ __

Ever had a negative HIV test? _ Yes _ No _ Unknown

Date of last negative HIV test *(if date is from a lab test with test type, enter in Lab Data section)* __ __ / __ __ / __ __ __ __

Number of negative HIV tests within 24 months before first positive test (# _____) _ Unknown

Section 9 Transition of Patients From Nonoccupational Postexposure Prophylaxis (nPEP) to Preexposure Prophylaxis (PrEP)

Two types of patients may be considered candidates for PrEP use after a course of nonoccupational postexposure prophylaxis (nPEP):

- Patients who request PrEP and also have had a possible sexual or injection drug-related HIV exposure in the prior 72 hours (i.e., are within the recommended window to start nPEP)
- Patients who request repeated courses of nPEP, particularly over a relatively recent period (e.g., more than twice during the past 6 months)

If evaluation demonstrates nPEP is clinically indicated and that the patient is also eligible for PrEP (e.g., behavioral risk for repeated HIV exposure, recent bacterial STI diagnosis in a sexually active person), then these patients should both be provided a 28-day course of nPEP and be evaluated for transition to PrEP at the conclusion of their nPEP course.

TRANSITIONING IMMEDIATELY FROM NPEP TO PREP

Transitioning from nPEP to PrEP without interruption at the completion of the 28-day nPEP course has the advantages of (1) maintaining satisfactory antiretroviral drug levels for PrEP (if nPEP adherence has been good); and (2) maximizing continuous prevention measures through continuity of nPEP to PrEP care. Essential steps include:

- At conclusion of 28 days of nPEP:
    - Repeat a rapid HIV test (ideally with a fourth-generation antigen/antibody assay) and assess for signs and symptoms of acute HIV infection.
    - If the rapid HIV test is positive or suspicion exists of possible acute HIV infection, draw blood for confirmatory testing and continue a 3-drug nPEP regimen pending confirmation of HIV status.
    - If HIV infection is confirmed, see Section 8 of Clinical Providers' Supplement for indicated next steps.
    - If the rapid HIV test is negative and no signs or symptoms of acute infection exist:
        - Stop the third medication in nPEP regimen and continue TDF/FTC daily as PrEP.
        - Complete any PrEP baseline laboratory testing not already performed as part of nPEP testing.
        - Provide medication adherence and risk-reduction support counseling.

- Complete any insurance/medication assistance paperwork required to cover PrEP medications (might be different than nPEP medications).
- Schedule follow-up visits for HIV, STI, and other laboratory testing as well as medication refills on the basis of standard PrEP clinical practice guidelines recommendations.

INITIATING PREP AT A LATER TIME

Deferring initiation of PrEP use can increase the period of risk for HIV acquisition because patients are left without the benefit of protective antiretroviral use. However, for some patients concluding a course of nPEP, additional time is needed to (1) make a decision about PrEP use; (2) perform additional clinical assessment and engage the patient in shared decision making in special medical circumstances, such as renal or liver impairment, pregnancy or breastfeeding; or (3) arrange and ensure coverage of medication costs, availability of continuity of PrEP care, or other logistic factors. Essential steps with this approach include:

- Reinforce the critical nature of safer sexual or injection drug use strategies while pending PrEP initiation
- Obtain baseline testing per PrEP guidelines
- Initiate PrEP, when possible

Consultation

Consultation with local or regional experts in nPEP and PrEP, or with the toll-free national PrEPline at 855-448-7737 or PEPline at 888-448-4911, can be sought for clinical scenarios requiring additional information or management options.

Section 10 Supplemental Counseling Information – Medication Adherence

MEDICATION EDUCATION AND ADHERENCE SUPPORT

Understanding what patients know about PrEP and why they are considering taking it can reveal important information about potential adherence facilitators or barriers. You may wish to begin discussion through a conversation (e.g., "Let's talk. Tell me what you know about PrEP" or "Why do you want to take PrEP?") that can help clarify whether the patient understands the risks and benefits of PrEP given their current sexual behavior and protection strategies, and how their reason(s) for taking PrEP may affect medication adherence.

Adherence to prophylactic regimens is strongly associated with patient understanding of drug information. Patients beginning a PrEP regimen need a very clear understanding of how to take their medications (i.e., when it is to be administered, how many pills to take at each dose) and what to do if they experience problems (e.g., how long outside the dosing window is a dose considered "missed", what to do if they miss a dose). Side effects are often a cause of non-adherence, so a plan for addressing them should be made. It is recommended that you and the patient develop a plan for addressing side effects that the patient would consider intolerable. The plan may include over-the-counter medications that can mitigate symptoms and should stress the need to use condoms consistently if the patient stops taking PrEP medication.

You should also discuss the need for the patient to be tested for HIV every 3 months. Although patients may feel anxious about such frequent testing, it is important that patients understand that frequent testing is needed to prevent drug resistance if they become infected while taking PrEP medication. Be prepared to answer other questions, such as,: "What if people see the medications and think I am HIV-positive?" "Do I need to tell my partner?" "Do I need to take the medication regularly when I am not having sex?"; "Will it help to take extra doses?" "How long can I take the medication?". When you begin a discussion around adherence, emphasize the normalcy of missing occasional doses and the importance of a plan to try to minimize missed doses (see Box 6.1 for an example of how to introduce this issue).

Box 6.1: Adherence Discussion

You are going to have to take the pill once a day, every day. Although this seems easy, we know that people forget to take their medicines, especially when they are not sick. It will be easier to take your medicine if you think through now some plans about how you'll do it. First, let's briefly discuss your experiences other times you might have taken medicine.

- *When you've taken medicines before, how did you remember to take them?
- Please tell me about any problems you had taking your pill.
- *What was most helpful for remembering to take them?

An adherence plan should include the following: (1) tailoring the dosing time to correspond with the patient's regularly scheduled activities so that medication taking becomes integrated into the patient's daily routine, (2) using reminders or technical devices (e.g., beepers, alarms) to minimize forgetfulness, (3) considering organizational needs and tools (e.g., calendars, strategies for weekends away from home) to address changes in routine and schedule, and (4) reviewing disclosure issues to identify those who can support the patient's intentions to adhere or barriers to adherence due to lack of disclosure/privacy at home. (See Box 6.2 for sample questions.)

Box 6.2: Developing an adherence plan

OK, now let's come up with a plan for taking your medicine.

1. Scheduling

What is your schedule like during a typical week day?
At what point in the day do you think it would be easiest to take the pill? That is, is there a time when you are almost always at home, and not in too much of a rush?
How does your schedule differ on weekends?

2. Reminder devices

How will you remember to take the pill each day?
One way to remember is to take the pill at the same time that you are doing another daily task, such as brushing your teeth or eating breakfast. Which of your daily tasks might be used for this purpose? Try to pick something that happens every day. Sometimes we might pick something that is not always done on the weekends or during other days, and then we are more likely to forget. (For example, … **One potential example follows**: sometimes I don't shave on Saturdays, but I always brush my teeth, so linking taking the medicine to brushing my teeth might be better than linking it to shaving.) It also helps to store the pills near the place where you perform this daily task.
Some people use a reminder device to help them remember. Do you have any reminder devices that you have used in the past? For example, watches, beepers, or cell phones.

3. Organizational skills

Where will you store the bottle of pills?
When you travel or spend the night outside of your home, what will you do about taking the pill?

4. Social support & disclosure

Who in your household will know the reason that you are taking the pills? Are they supportive of you taking them? Are there individuals who might make assumptions about your serostatus because you have these medicines?

You may wish to explore other potential barriers that emerged in initial conversations (e.g., beliefs and attitudes), including factors (e.g., as substance use, depression or unstable housing) known to negatively affect medication adherence, such. To adhere to PrEP medication well, some patients may need access to mental health or social services.

MONITORING PREP PATIENTS: ASSESSING SIDE EFFECTS AND ADHERENCE

Assess medication adherence as well as adherence to HIV testing at every visit. Self-reported adherence is typically an overestimate of true adherence, but patients may over report their adherence when they fear that a more accurate report would results in a negative judgment from their clinician. When asking patients about their adherence, do your best to adopt a non-judgmental attitude, giving the patient permission to share adherence difficulties without worrying that you will reproach them. Asking patients to help you understand how they are doing with their medications will provide more information and thus allow for a better diagnostic picture of a patient's needs than will a more prescriptive approach.

Begin follow-up visits by asking the patient how well they have been doing with taking all of their medicines as scheduled. Accept more general responses (e.g., "so so", "pretty good", "excellent", "perfect") before asking for specific information about the frequency and the context of missed doses. Provide reinforcement for patients who report that they are doing well: ask questions such as "What are you doing to keep this going so well?" or "That's great. Can you see anything getting in the way of this?" These exchanges can help solidify the factors that are supporting your patients' adherence while helping them prepare for any barriers that may arise in the future.

When talking with patients who are not reporting perfect adherence, ask as to how many doses they have missed during a specific period. Assessing a longer period (e.g., 30 days, 7 days) is preferred to shorter periods (e.g., 3 days), not only because adherence can vary with changes in schedule (e.g., weekends, holidays) that may not have occurred during the shorter assessment period, but because many patients increase medication-taking just before medical appointments, a phenomenon supported by blood level assessments in the iPrEx trial.[2] When asking about many doses were missed (e.g., "In the last 30 days, how many times have you missed your PrEP medication?"), also (1) ask whether this was typical since their last clinic visit in order to gain a sense of adherence patterns, (2) ask for specific information about when they most recently missed dose(s), and (4) determine the circumstances during which those missed doses occurred (e.g., "Where were you?" "Who were you with?" "What happened just before you were supposed to take your medicine?"). Asking what happened on the day the dose was missed, and getting the patient's perspective on what generally gets in the way of taking medications regularly, will facilitate a conversation that will help to identify the patient's specific adherence barriers as well as the type of adherence support the patient needs.

On the basis of this conversation, develop a plan to address adherence barriers. Questions such as "What do you think you can do differently?" "What things make it easier to take your medications?" "What things need to happen for you to take your medications regularly?" or "What might you try [to not forget your weekend doses]?" bring the patient into the planning process and thus facilitate identification of the strategies most likely to be implemented. It's important for you to be familiar with a range of adherence strategies that can be shared with patients who require help with this task.

Finally, assess whether the patient is experiencing any side effects of medication, the severity of the side effects, and their role as an adherence barrier determined. Currently, most of what is

known about antiretroviral therapy (ART) side effects is derived from patients with HIV. Healthy people may be more concerned about side effects than HIV patients. Try to determine whether clinical symptoms attributed to PrEP medication could possibly be due to other disorders (e.g., depression) or natural processes (e.g., aging). If necessary, include medications to treat side effects in the adherence plan.

Section 11 Supplemental Counseling Information – HIV Risk Reduction

Determining whether the patient is a good candidate for PrEP is not strictly objective, and should be based on an ongoing discussion between you and your patient. Risk screening can be conducted using various approaches: face-to-face interviews, written forms, or computer-based tools. Written forms and computer-based tools are effective and can be conducted with fewer staff resources[33]. However, self-administered written forms are not recommended for persons with low literacy.

Using risk screening information and the HIV test results, provide your patients with services that are appropriate for their level of risk and are tailored to their prevention needs. Patients who report no or few risk factors, may have minimal prevention needs. In the absence of other information, these patients do not need PrEP. For patients for whom PrEP is appropriate, provide risk-reduction counseling and support services before, during, and after PrEP you prescribe PrEP.

Sexual Risk Reduction Counseling

Address the sexual health of your patients, including risk behaviors that increase the likelihood of acquiring HIV or other sexually transmitted infections. Several discussion areas are recommended even in brief discussions of sexual risk behavior. For patients who demonstrate an elevated risk of sexual HIV acquisition, provide a brief risk reduction intervention onsite or link them to a program that provides those services (see http://www.effectiveinterventions.org). For patients who are continuing to engage in high-risk sexual behaviors or who need additional prevention services (beyond a brief risk-reduction intervention), link them to a program that provides more intense interventions, such as those in the Compendium of Evidence-based HIV Prevention Interventions (see http://www.cdc.gov/hiv/topics/research/prs/evidence-based-interventions.htm) which are often provided by local health departments or community-based organizations. These patients may also be good candidates for continued use of PrEP until they are consistently practicing effective behavioral risk reduction.

- Counseling patients who test HIV-negative. Guidelines have emphasized the importance of risk-reduction counseling for persons determined to be at substantial risk of sexual HIV acquisition[34]. It is recommended that you select the most appropriate brief sexual risk-reduction intervention that can address the immediate prevention needs of HIV-negative patients at substantial risk for acquiring HIV infection. One counseling approach designed for STD clinic providers, the RESPECT model[35], can be used. The model consists of two brief, 20-minute, interactive, patient-focused counseling sessions that are conducted during HIV testing, and have been found to significantly reduce sexual risk behaviors and prevent new STDs among HIV-negative patients (although not HIV incidence). Besides RESPECT, there are now several other effective brief sexual risk-reduction intervention models that should be considered when providing HIV-negative

patients appropriate prevention counseling. Although no brief counseling models have yet proven effective for patients taking PrEP, some of the models developed for persons with HIV infection, (Partnership for Health[36], and motivational interviewing[37,38)] may be appropriate for adaptation to counseling patients who are taking PrEP.

Intensive sexual risk reduction interventions may be appropriate for some patients, who should be referred to appropriate providers. In general, HIV risk-reduction interventions have been shown through numerous systematic reviews, to be efficacious in reducing HIV sexual risk behaviors, promoting protective behaviors, and reducing the incidence of new sexually transmitted infections among high-risk populations from various demographic, racial/ethnic, or behavioral risk groups[39,40].

- Counseling patients who test HIV-positive. Provide emotional support and counseling to patients who receive preliminary or confirmed positive HIV test results to help them understand the test result, the benefits of initiating and remaining in HIV medical care, and the importance of reducing their HIV-related sexual and/or injection risk behaviors to help protect their health and the health of their partners. Link all HIV-positive patients to HIV medical care, prevention services that routinely offer risk screening and ongoing risk-reduction interventions, and other health services as needed.

PrEP Follow-up Visits

Provide brief behavioral HIV risk assessment and supportive counseling at each follow-up visit while the patient is taking PrEP medication. For important components of these sessions, see Box 7.1. At least annually discuss with the patient whether discontinuation of PrEP is warranted. If the decision is made to discontinue PrEP, a plan for periodic reassessment should be made and any indicated referrals to community programs or other support services should be arranged.

Box 7.1: Elements of brief HIV risk-reduction counseling in clinical settings

- Create and maintain a trusting and confidential environment for discussion of sexual or substance abuse behaviors.
- Build an ongoing dialogue with the patient regarding their risk behavior (and document presence or absence of risk behaviors in the confidential medical record).
- Reinforce the fact that PrEP is not always effective in preventing HIV infection particularly if used inconsistently, but that consistent use of PrEP together with other prevention methods (consistent condom use, discontinuing drug injection or never sharing injection equipment) confers very high levels of protection.

Section 12 PrEP-Related ICD, CPT and LOINC codes

ICD-10 codes	Description
Z20	Contact with and (suspected) exposure to communicable diseases
Z20.2	Contact with and (suspected) exposure to infections with a predominantly sexual mode of transmission
Z20.5	Contact with and (suspected) exposure to viral hepatitis
Z20.6	Contact with and (suspected) exposure to human immunodeficiency virus (HIV)
Z20.828	Contact with and (suspected) exposure to other viral communicable diseases
Z77.21	Contact with and (suspected) exposure to potentially hazardous body fluids
W46	Contact with hypodermic needle: "the appropriate 7th character is to be added to each code from category W46" A- initial encounter, D- subsequent encounter, S-sequela
W46.0	Contact with hypodermic needle (hypodermic needle stick NOS)
W46.1	Contact with contaminated hypodermic needle
Z20.8	Contact with and (suspected) exposure to other communicable diseases
Z20.81	Contact with and (suspected) exposure to other bacterial communicable diseases
Z79	Long term (current) drug therapy. Includes long term (current) drug use for prophylactic purposes
Z51.81	Therapeutic drug level monitoring
Z51.89	Encounter for other specified aftercare
Z79.899	Other long term (current) drug therapy
B20	Human immunodeficiency virus (HIV) disease. Includes: AIDS; AIDS-related complex (ARC); HIV infection, symptomatic
Z21	Asymptomatic human immunodeficiency virus (HIV) infection status
B16.9	Acute hepatitis B without delta-agent and without hepatic coma
B16.1	Acute hepatitis B with delta-agent without hepatic coma
B17.0	Acute delta-(super) infection of hepatitis B carrier
Z22.51	Carrier of viral hepatitis B
B18.0	Chronic viral hepatitis B with delta-agent
B18.1	Chronic viral hepatitis B without delta-agent
B16.0	Acute hepatitis B with delta-agent with hepatic coma
B16.2	Acute hepatitis B without delta-agent with hepatic coma
Z00.0	Encounter for general adult medical examination
Z01.812	Encounter for preprocedural laboratory examination (blood and urine tests prior to treatment or procedure)
Z11.3	Encounter for screening for infections with a predominantly sexual mode of transmission
Z11.4	Encounter for screening for human immunodeficiency virus (HIV)
Z11.59	Encounter for screening for other viral diseases
Z11.8	Encounter for screening for other infectious and parasitic diseases
Z13.89	Encounter for screening for other disorder (encounter for screening for genitourinary disorders)
Z13.9	Encounter for screening unspecified

ICD-10 codes	Description
Z32.0	Encounter for pregnancy test
Z70.0	Counseling related to sexual attitude
Z70.1	Counseling related to patient's sexual behavior and orientation
Z70.3	Counseling related to sexual behavior and orientation of third party (child, partner, spouse)
Z72.5	High risk sexual behavior
Z72.51	High risk heterosexual behavior
Z72.52	High risk homosexual behavior
Z72.53	High risk bisexual behavior

Sources: http://www.cdc.gov/nchs/icd/icd9cm.htm and http://www.cdc.gov/nchs/icd/icd10cm.htm

CPT Codes	Description
4276F	Potent antiretroviral therapy prescribed (HIV)
4270F	Patient receiving potent antiretroviral therapy for ≥6 months (HIV)
4290F	Patient screened for injection drug use (HIV)
4293F	Patient screened for high-risk sexual behavior (HIV)
86701	HIV antibody test performed (HIV-1 only)
86703	HIV antibody test performed (HIV-1 and HIV-2)
87389	HIV-1 EIA antibody with HIV1&2 antigens
87390	HIV-1 detection by immunoassay (IAAD EIA HIV-1)
87534	HIV-1 detection by nucleic acid, direct probe
87535	HIV-1 detection by nucleic acid, amplified probe
87536	HIV-1 quantitation
87900	Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics
87901	HIV-1 genotype by nucleic acid (RNA or DNA)
80074	Hepatitis panel
86704	HBcAb
86705	HBcAb, IgM antibody
87340	HBsAg
87517	Hepatitis B quantitation

Source: http://online.statref.com/titleinfo/fxid-24.html

LOINC Codes				
Order Test Number	Order Test Name	Result Test Number	Result Test Name	Result LOINC Code
0020025	Creatinine, Serum or Plasma	0020025	Creatinine, Serum or Plasma	2160-0
0020144	Renal Function Panel	0020025	Creatinine, Serum or Plasma	2160-0
0020399	Basic Metabolic Panel	0020025	Creatinine, Serum or Plasma	2160-0
0020408	Comprehensive Metabolic Panel	0020025	Creatinine, Serum or Plasma	2160-0
0085024	CTT Chemistry 20 Profile	0020025	Creatinine, Serum or Plasma	2160-0
0085025	CTT Chemistry 27 Profile	0020025	Creatinine, Serum or Plasma	2160-0
0020089	Hepatitis B Surface Ag w/ Reflex to Conf	0020089	Hepatitis B Surface Antigen	5196-1
0020090	Hepatitis B Virus Surface Antibody	0020090	Hepatitis B Surface Antibody	5193-8
0020091	Hepatitis B Virus Core Antibodies, Total	0020091	Hepatitis B Core Antibodies, Total	13952-7
0020092	Hepatitis B Virus Core Antibody, IgM	0020092	Hepatitis B Core Antibody, IgM	24113-3
0020128	Hepatitis B Virus Surface Ag, Confirm	0020128	Hepatitis B Surface Antigen Confirmation	7905-3
0020454	Hepatitis Panel, Chronic HBV	0020089	Hepatitis B Surface Antigen	5196-1
0020454	Hepatitis Panel, Chronic HBV	0020522	Chronic Hepatitis B Panel Interpretation	45159-1
0020454	Hepatitis Panel, Chronic HBV	0020090	Hepatitis B Surface Antibody	5193-8
0020457	Hepatitis Panel, Acute	0020092	Hepatitis B Core Antibody, IgM	24113-3
0020457	Hepatitis Panel, Acute	0020179	Acute Hepatitis Panel Interpretation	13169-8
0020457	Hepatitis Panel, Acute	0020089	Hepatitis B Surface Antigen	5196-1
0056025	Hepatitis B Virus DNA Quant RT- PCR	0051820	HBV DNA Interpretation	29610-3
0056025	Hepatitis B Virus DNA Quant RT- PCR	0056026	HBV DNA (log IU/mL)	48398-2
0056025	Hepatitis B Virus DNA Quant RT- PCR	2002322	HBV DNA (IU/mL)	42595-9
2001567	Hepatitis B Virus Genotype	2001569	Hepatitis B Genotype	32366-7
2001567	Hepatitis B Virus Genotype	2001569	Hepatitis B Genotype	32366-7
2006526	HIV-1,2 Combo Ag/Ab EIA w/Reflex	2006611	HIV-1,2 Combo Antigen/Antibody	56888-1
2007980	HIV-1,2 Combo Ag/Ab EIA w/Reflx	2007986	HIV Interpretation	69668-2
2007980	HIV-1,2 Combo Ag/Ab EIA w/Reflx	2007982	HIV-1/HIV-2 Antibody Differentiation	42768-2
2007980	HIV-1,2 Combo Ag/Ab EIA w/Reflx	2007985	_HIV-2 Antibody by Multispot	30361-0

LOINC Codes				
Order Test Number	Order Test Name	Result Test Number	Result Test Name	Result LOINC Code
2007980	HIV-1,2 Combo Ag/Ab EIA w/Reflx	2007984	_HIV-1 Antibody by Multispot	29893-5
2007980	HIV-1,2 Combo Ag/Ab EIA w/Reflx	2007981	HIV 1,2 Combo Antigen/Antibody	56888-1
0020284	HIV 1 Antibody Confirm, Western blot	0020284	HIV-1 Antibody Confirm, Western blot	5221-7
0020698	HIV-1 Ab Confirm, Western blot w/Reflex	0020284	HIV-1 Antibody Confirm, Western blot	5221-7
2005375	HIV-1 w/Reflex to HIV-1 Western blot	2005376	HIV-1 Antibody	29893-5
0051250	HIV-2 Antibody w/Reflex to Supplemental	2008282	HIV-2 Antibody, Supplemental	30361-0
0051250	HIV-2 Antibody w/Reflex to Supplemental	0051251	HIV-2 Antibody by ELISA	30361-0
0093061	HIV-1 PCR, Qualitative	0093062	HIV-1 PCR, Qualitative	44871-2
0093061	HIV-1 PCR, Qualitative	0093062	HIV-1 PCR, Qualitative	44871-2
0020466	HIV 1 RNA Quantitative by bDNA	0020464	HIV-1 RNA Quant bDNA, Log	29539-4
0020466	HIV 1 RNA Quantitative by bDNA	2002687	HIV-1 RNA Quant bDNA, Copy	23876-6
0055598	HIV-1 RNA Qnt By Real-Time PCR	0051817	HIV-1 RNA Qnt Real-Time PCR Interp	24013-5
0055598	HIV-1 RNA Qnt By Real-Time PCR	2002646	HIV-1 RNA Qnt Real-Time PCR, Copy	20447-9
0055598	HIV-1 RNA Qnt By Real-Time PCR	0020297	HIV-1 RNA Qnt Real-Time PCR, Log	29541-0
2002688	HIV-1 RNA Quant bDNA reflex to Genotype	0020464	HIV-1 RNA Quant bDNA, Log	29539-4
2002688	HIV-1 RNA Quant bDNA reflex to Genotype	2002687	HIV-1 RNA Quant bDNA, Copy	23876-6
2002689	HIV-1 RNA Quant reflex to Genotype	0051817	HIV-1 RNA Qnt Real-Time PCR Interp	24013-5
2002689	HIV-1 RNA Quant reflex to Genotype	2002646	HIV-1 RNA Qnt Real-Time PCR, Copy	20447-9
0051186	HIV 1, vircoTYPE	0055648	Vircotype Information	45182-3
0051186	HIV 1, vircoTYPE	0055648	Vircotype Information	45182-3
0055670	HIV-1 Genotyping	0051722	HIV-1 Genotyping	49659-6
0055670	HIV-1 Genotyping	2002141	EER HIV-1 Genotyping	11526-1
0055670	HIV-1 Genotyping	0051722	HIV-1 Genotyping	49659-6
0055670	HIV-1 Genotyping	2002141	EER HIV-1 Genotyping	11526-1
2004331	HIV GenoSure MG	0092073	Viral Load - RT	8251-1
2004331	HIV GenoSure MG	0092074	Viral Load Date - RT	19151-0

Source: http://loinc.org/

Section 13 Potential Practice Quality Measures[37,38]

Primary (Outcome) Measures

Quality Indicator	Eligible Population	Numerator	Denominator
HIV testing, baseline	All persons prescribed PrEP medication	Number of patients with negative HIV test result documented within 1 week prior to initial prescription of PrEP medication	Number of persons prescribed PrEP
HIV testing, interval	All persons prescribed PrEP medications	Number of PrEP patients with an HIV test result documented at least every 3 months while PrEP medication prescribed	Number of persons prescribed PrEP for >3 months continuously
PrEP medication adherence	All persons prescribed PrEP medications	Number of PrEP patients with adherence assessment noted in the medical record for any visits when prescribed PrEP medication	Number of persons prescribed PrEP medication
Seroconversion	All persons prescribed PrEP medications	Number of patients with a confirmed HIV positive test result while PrEP medications prescribed	Number of persons prescribed PrEP medication for >1 month
Seroconversion, resistant virus	All persons prescribed PrEP medication who received a genotypic resistance test within 4 weeks after an HIV positive test result	Number of persons seroconverting while taking PrEP who have resistant virus detected by genotypic test	Number of persons prescribed PrEP medication who received a genotypic resistance test within 4 weeks after a confirmed HIV positive test result

Section 14 Methods for Developing the PrEP Clinical Practice Guideline

In 2009, in recognition of the lead time needed to develop clinical guidance for the safe and effective use of PrEP should clinical trials results support it, CDC initiated a formal guidelines development process to allow for early review of the relevant literature, discussion of potential guidelines content given scenarios of potential trial results, and fostering the development of expert and stakeholder consensus. This process was designed to provide a basis for the rapid issuance of interim guidance, to be followed by Public Health Service guidelines as soon as the earliest trial findings indicated sufficient PrEP efficacy and safety to merit its implementation for HIV prevention through one or more routes of transmission.

This guidelines development process was based on a review of experience with the development of other clinical and nonclinical guidelines at CDC, including those for STD treatment and antiretroviral prevention of mother-to-child transmission following the ACTG 076 trial results.

There were five basic components to the process for developing the 2014 PrEP guidelines:

1. An **HHS Public Health Service (PHS) Working Group** to develop interagency consensus on major points of implementation policy and provide agency review of guidelines. This working group included representatives from agencies that would formally clear PHS guidelines (FDA, HRSA, NIH, HHS/OHAP) as well as agencies that may implement such guidance (IHS, VA).
2. A **CDC writing team** responsible for preparing draft guidance documents based on the recommendations of the other groups involved in the guidelines process
3. A number of **external work groups** responsible for considering specific sets of issues for the planned guidance. Each work group was composed of 5-8 members representative of the following:
    - Members of the academic community and scientists with expertise in the content area to ensure that the guideline elements are science-based
    - Health department and clinical users of the guidelines to ensure the feasibility of implementing guideline elements in local and state HIV prevention programs
    - At least one advocate or community-based organization member with personal or professional experience in the content area to serve as an ongoing bridge to community discussions and to supplement the advocate input received by other activities.
    - Geographic diversity (multiple US regions and small/medium/large jurisdictions)
    - Experience with PrEP issues when possible

    External work groups were convened to consider the following areas:
    - Clinical care guidance
    - Clinic-based counseling guidance
    - Integrating PrEP with other prevention services
    - Persons potentially exposed by injection drug use
    - MSM
    - Women
    - African American, Hispanic/Latino, and other heterosexual men
    - Adolescents

In addition to these standing work groups, technical expert panels were convened to inform guidelines for PrEP use in the following areas:

- Public health and clinical ethics
- Monitoring and evaluation framework
- Financing and reimbursement issues
- Preconception and intrapartum use of PrEP
- Public health legal and regulatory issues
- Issues relevant to benefits managers and insurers

4. A series of **stakeholder web/phone conferences** were held to receive input on questions, concerns, and preferences from a variety of perspectives including those of community-based organizations, state and local AIDS offices, professional associations, and others.
5. After the publication of the first efficacy trial results, a **face-to-face consultation** of external experts, partners, agencies, and other stakeholders was held to consider the recommendations for guidance made by the above groups and to discuss any additional ideas for inclusion in PrEP guidelines.

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The working groups and expert panels listed here were convened by teleconference before trial results were available (2009-2010) and some were reconvened after each trial results for each population group were published. As technical experts, prevention partners, and key stakeholders, they were asked to assist us to identify relevant scientific/medical literature and share thoughts on topics that would inform the

development of possible future guidelines for PrEP use in the US. They did not participate in the writing of these guidelines. No financial disclosures were sought. See Clinical Providers' Supplement section 14 for a description of the criteria use for constitution of the working groups and expert panels. Institutional associations listed for participants are those at the time of the group discussions and may have changed since.

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Potential conflicts of interest:

CDC and individual employees involved in the guideline development process are named in US government patents and patent applications related to methods for HIV prophylaxis.

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This process allowed wide input, transparency in discussing the many issues involved, time for the evolution of awareness of PrEP and ideas for its possible implementation, in addition to facilitating the development of a consensus base for the eventual guidance. At the same time, it allowed for guidelines based on expert opinion, and recommendations deemed feasible by clinical providers and policymakers.

On the basis of results from the first 4 activities listed above and the publication in late November 2010 of results from the first clinical trial to show substantial efficacy and safety[2], CDC issued interim guidance for PrEP use among men who have sex with men in January 2011.

This interim guidance was followed by a face-to-face meeting of external in May 2011. As efficacy and safety results were published, additional interim guidance documents were issued for heterosexually active adults (August 2012) and injection drug users (July 2013).

SYSTEMATIC LITERATURE REVIEW METHODS

For the 2014 guidelines, a systematic review was conducted of PrEP studies published from January 2010 through December 2013. For the 2017 guidelines, the same search strategy was run to update studies published through June 2017. Searches were conducted of MEDLINE, Embase, CINAHL, and Cochrane Library databases. The search strategy used the following criteria:

- Pre-Exposure Prophylaxis/ OR Chemoprevention/ OR (((Preexposure OR Pre-exposure) adjacent to prophylaxis) OR PrEP OR (topical adjacent to (prevention OR prophylaxis OR microbicide* OR gel OR pericoital OR precoital OR vaginal OR rectal OR anal)) OR chemoprophylaxis OR chemoprevention OR chemo-prophylaxis OR chemo-prevention OR iPrEX).mp.
- AND
- (exploded terms) Anti-HIV Agents/ OR Anti-Retroviral Agents/ OR HIV Infections/pc OR ((HIV OR human immunodeficiency virus) AND (antiretroviral* OR anti-retroviral* OR antiretrovirus* OR anti-retrovirus* OR Truvada OR tenofovir OR emtricitabine OR (TDF ADJ5 FTC)))
- AND NOT animals
- in the title, abstract, keyword heading word, subject heading fields

Retrieved citations were provided in an Endnote reference file for deduplication. Then 2 scientists independently reviewed the citations and removed those that were not published in English, did not contain data (e.g., editorials, reviews, news reports), or did not contain data about oral TDF/FTC for PrEP. The next step was to screen citations to remove those that did not contain new data about oral PrEP (data/analyses not previously published). For the 2017 update, year of publication, author, and titles were compared with the 2014 Endnote library as necessary to identify already exiting entries. During this step, abstracts or full articles were read and publications were categorized into the following groups.

- New clinical trial results
- New human observational study results
- New survey, focus group, or other behavioral study results
- New cost analysis results (e.g., program cost, cost benefit analysis)
- New modeling results (e.g., impact models)
- New laboratory human study results (e.g., drug levels, resistance)
- None of the above

The coding by the two reviewers was then compared and discrepancies were reconciled. Citations with no new data about daily oral PrEP with TDF/FTC were deleted from the updated Endnote 2017 library.

Data from the clinical trial, human observational study, and laboratory human study results were added to the evidence tables. Study findings presented in the evidence tables were each assessed for quality of the study using GRADE criteria[39] (see guidelines Appendix 1, Table 13). Then all data supporting a specific recommendation were given a summary strength of evidence rating (across all studies relevant to that recommendation) using the same system as used for the DHHS antiretroviral treatment guidelines[32] (see PrEP clinical practice guidelines Appendix 1, Table 12).

DRAFT GUIDELINE WRITING AND REVIEW PRIOR TO PUBLICATION

The draft was written to address guidelines standards for review of the strength of evidence (GRADE approach[41]) as well as a format designed to promote guideline implementation (GLIA [42]), dissemination (GEM[43]), and adoption (AGREE[44,45]).

The 2014 draft clinical practice guideline and clinical providers supplement were reviewed by CDC, FDA, NIH, HRSA, and HHS, and a series of webinars were held in 2012 and 2013 to obtain additional expert opinion and public engagement on draft recommendations for PrEP use. The draft guideline and supplement were then reviewed by a panel of 6 external peer reviewers who had not been involved in their development. At each step, revisions were made in response to reviewer and public comments received.

For the 2017 update, the 2014 systematic review of published literature was updated through June 2017. Although no changes to the graded recommendations were indicated, additions to the evidence review tables were made; minor clarifying edits to the supporting text were made to enhance consistency with recently updated STD, nPEP, and perinatal guidelines sections relevant to PrEP; and updated references were added. These changes were shared with a group of 4 external peer reviewers for comment.

Plans for Updates to the Guideline

PrEP is a rapidly changing field of HIV prevention with several additional clinical trials and studies are now underway or planned. Updates to these guidelines are anticipated as studies provide new information on PrEP efficacy, HIV testing, drug levels, adherence, longer term clinical safety, and changes in HIV risk behaviors associated with PrEP medication use for HIV uninfected MSM, heterosexuals, injection drug users, pregnant women and their newborns; as well as information on the efficacy and safety of other antiretroviral medications, and other routes and schedules of medication delivery for PrEP.

When significant new data become available that may affect patient safety or graded recommendations for PrEP use, an announcement with suggested revisions to the existing guidelines will be posted on the CDC web site and the public will be given a 2-week period to submit comments. These comments will be reviewed and a determination made as to whether additional revisions are indicated. Final updated guidelines will then be posted on the CDC web site.

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