



Frequently Asked Questions (FAQs)

Research Rationale

1. What does PrEP stand for?

There is scientific evidence that antiretroviral (anti-HIV) medications may be able to play an important role in reducing HIV risk. Two antiretroviral medications – tenofovir disoproxil fumarate (also known as tenofovir) and a combination of tenofovir and emtricitabine (FTC) – taken as daily preventive therapy, might substantially reduce the risk of HIV. This approach is known as pre-exposure prophylaxis, or PrEP:

- **Pre** means *before*
- **Exposure** - *coming into contact with HIV*
- **Prophylaxis** – *taking medication to prevent becoming HIV infected*

2. Why conduct a study of pre-exposure prophylaxis?

Safe and effective approaches to preventing new HIV infections are urgently needed. An estimated 7,400 people a day are being infected with HIV, according to UNAIDS. More than 60 million people have been infected with HIV since the pandemic began. AIDS resulting from HIV infection is the leading cause of death in Africa, and the fourth leading cause of death globally. Traditional prevention methods, including abstinence, being faithful to one sexual partner, and using condoms (the ABC's of HIV prevention), are well known; however, not everyone is able to use these methods all of the time.

Women are especially vulnerable. The majority of HIV infections in Africa occur among women. For many women, the current prevention methods are inadequate, since they often do not have the social or economic power to refuse sex or negotiate condom use.

A vaccine against HIV is most likely more than 10 years away. Thus, new prevention strategies must be found.

3. How might PrEP work to protect against HIV infection?

The idea of providing a medication to prevent an infection is not new. One example is that of mothers who are infected with HIV, who take medications during pregnancy to prevent passing HIV to their babies at birth. Another example is that of travelers who take medication to prevent malaria. Key to both of these examples is that the medication is in the bloodstream before exposure to the infection, so that it is ready to prevent disease from happening.

For PrEP, we think that, if medications are in the bloodstream when someone is exposed to HIV, then the virus will not be able to establish itself and infect the person.

4. What is the evidence that PrEP might work?

Several lines of evidence suggest that PrEP might work:

- The likelihood of transmitting HIV from mother to child can be halved or more with anti-HIV medications taken during pregnancy, delivery, and after birth.
- Anti-HIV medications can decrease the risk of an adult getting HIV after an accidental exposure to HIV – for example, a health care worker accidentally stuck by a needle.
- Animal studies have shown that PrEP, using tenofovir or the combination emtricitabine/tenofovir, substantially protects monkeys exposed repeatedly to an HIV-like virus.
- A large phase III efficacy trial of PrEP for the prevention of HIV infection in men who have sex with men found that oral combination emtricitabine/tenofovir was both safe and effective when used with other risk reduction measures. More research is needed to confirm these results in other populations.

Although these lines of evidence are very encouraging, we do not know for sure that PrEP works to prevent HIV infection in humans. That is why PrEP needs to be studied.

5. Is the medicine safe?

The safety of tenofovir and combination emtricitabine/tenofovir have been established in large clinical studies and in medical settings. Tenofovir was first licensed for use as an HIV treatment in 2001 and combination emtricitabine/tenofovir for use as an HIV treatment in 2004. More than 430,000 HIV-infected persons worldwide have used these medications and they are highly effective. Both of these medications are licensed for use in Kenya and Uganda.

When used for HIV treatment, tenofovir and combination emtricitabine/tenofovir are generally very well tolerated and have few side effects. When side effects do occur, the most common ones from tenofovir are nausea, vomiting and loss of appetite. Those of combination emtricitabine/tenofovir are nausea, vomiting, diarrhoea, headache and rash.

Several studies of the safety of tenofovir used for PrEP have been completed. One study, conducted by Family Health International, involved more than 900 women in Ghana, Cameroon, and Nigeria. It showed that PrEP was safe to give to HIV uninfected women in Africa. These women had very few side effects and no serious side effects as a result of PrEP use. An extended safety study of oral tenofovir among men who have sex with men from the US was completed by the Centers for Disease Control and Prevention. It showed that tenofovir PrEP was safe and did not increase the risk of serious adverse effects. Neither of these two studies was large enough to measure whether oral tenofovir prevented HIV infection. However, a large phase III efficacy trial of PrEP for the prevention of HIV infection in men who have sex with men found that oral combination emtricitabine/tenofovir was both safe and effective when used with other risk reduction measures. More research is needed to confirm these results in other populations.

6. How is PrEP different than HIV treatment?

With PrEP, a person who does not have HIV infection takes anti-HIV medication to prevent from getting HIV. This is different than HIV treatment. HIV treatment is given to persons who already have HIV, often when they develop symptoms of AIDS, to decrease the amount of virus. Treating persons who already have HIV has substantial health benefits, but no treatment cures HIV. HIV treatment usually consists of a combination of three or more anti-HIV medications. This can be costly and can result in more side effects. In contrast, fewer

drugs (i.e., one or two anti-HIV medications) may be needed to prevent HIV, and so could have fewer side effects and be less costly.

7. What studies of PrEP are being done?

Four large studies are currently being conducted to test whether PrEP can prevent HIV infection. These studies are being done in up to 12 countries worldwide – they involve men and women, in Africa, Asia, South America, and the United States. These studies will involve more than 19,000 study participants.

Partners PrEP Study

8. What is the Partners PrEP Study?

The University of Washington is working with collaborators in Kenya and Uganda to conduct a study, called the Partners PrEP study, to see if PrEP prevents HIV. The study involves volunteers who are HIV discordant couples – that is, where one partner has HIV and the other does not have HIV. The partner who does not have HIV takes the anti-HIV medication daily. The objective of the study is to see whether having this medication in the bloodstream prevents the HIV uninfected partner from getting HIV. The study started in July 2008 and finished recruiting participants in December 2010. Results are expected in 2013. The study is led by the University of Washington and is funded by the Bill & Melinda Gates Foundation.

9. In a couple, how can one partner have HIV and the other partner not have HIV?

HIV discordance in couples is very common. Studies in Africa have found that the partner of an HIV infected person has about a 50% chance of being HIV uninfected, even if the couple has been together for several years. In the Partners PrEP Study, all the couples are in stable relationships, and most are married.

The factors that lead some couples to be HIV discordant are not well understood. Some of these factors include higher HIV levels, genital herpes, and the male partner being uncircumcised. Many couples have been in relationships for years and may not know each other's HIV status. In spite of this, however, the HIV uninfected partner in a discordant couple can become infected at any time. In fact, stable couples that are HIV discordant are thought to account for the majority of new HIV infections among adults in Africa. Thus, HIV uninfected individuals within HIV discordant couples are at considerable risk for getting HIV.

10. Do HIV discordant couples stay together?

Couples HIV counselling and testing provides an opportunity for couples to learn their HIV status together. They are counselled about risk reduction, positive living, and disclosure. They are able to plan for the future together, while avoiding blame and learning how to cope with HIV discordance.

Many HIV discordant couples want to stay together. They have built lives together, love each other and may have children together. Importantly, they want to find ways to protect the uninfected partner from getting HIV.

11. How is the Partners PrEP Study designed?

The Partners PrEP study includes 4,758 HIV discordant couples, enrolled at 9 clinical sites in Uganda and Kenya. The study is a randomized, double-blind placebo-controlled clinical trial. The participants who are not HIV infected were randomly divided into groups by a computer. The participants take their medication every day. Those from one group take tenofovir, a second group takes combination emtricitabine/tenofovir, and the third group

takes a placebo. The medications look and taste alike so that it is impossible to tell the difference between the placebo and active medications.

12. What is a placebo and why is it necessary?

A placebo is an inactive tablet that has no medicine in it that looks, tastes, and feels exactly like tenofovir or combination emtricitabine/tenofovir. In research studies, the medicine being tested is compared with a placebo to see if the effects are truly due to the medication itself or merely due to chance. The control group, the participants who received a placebo, are compared to the treatment group, the participants who received the active medicine being tested. The results from the groups are analyzed to see if the medicine is truly effective in preventing HIV infection.

The placebo is necessary because we do not know if PrEP truly works to prevent HIV infection in humans, and so we have to compare the number of participants who get HIV during the study among those who receive PrEP against the number of participants who get HIV among those who receive placebo. None of the study staff, or the participants themselves, know who is receiving the placebo tablets. This is to allow an accurate assessment of whether PrEP really works.

13. Why study two different medicines?

Both tenofovir and combination emtricitabine/tenofovir are safe and effective treatments for persons who have HIV. However, we need to know whether tenofovir alone or tenofovir in combination with emtricitabine are effective in **preventing** HIV infection. Two medications might be better than one, or tenofovir alone might be just as good as combination emtricitabine/tenofovir for preventing HIV. At the same time, two medications might cause more side effects than one. Because we don't know the answers to these questions, it is essential to evaluate both of these promising prevention strategies.

14. Who is eligible to participate in the Partners PrEP study?

The study has enrolled volunteers who are sexually active HIV discordant couples. To protect the health of the study participants, both the HIV uninfected and the HIV infected partner in a couple met strict eligibility requirements. The HIV uninfected partner was healthy, with normal liver, kidney and blood count tests, and cannot be taking certain medications that might interact with the study medications. The HIV uninfected partner also cannot be pregnant or breastfeeding. The HIV infected partner was in good health, having a CD4 count over 250 cells/mm³ and ineligible for treatment with HIV anti-retroviral medications by national guidelines. Participants will be in the study for up to three years. Participation in the study is voluntary.

15. What sort of counselling will the study participants receive?

- HIV uninfected participants are counselled to take their medications every day and to report to the staff any possible side effects they might experience. At every monthly visit, counselors work with participants to strategize ways to remember to take the study medication every day, as it is very important that drugs are taken correctly or we will not be able to find out if PrEP works to prevent HIV infection.
- At every visit, HIV uninfected participants also have counseling about not sharing their study medications with anyone else, including their HIV infected partner.
- All participants in the Partners PrEP Study receive intensive counseling, both individually and as a couple, about how to avoid getting HIV, how to live together as an HIV discordant couple, and about the study purpose and procedures. Counselling occurs as part of every study visit.

- HIV infected participants in the study also receive counseling about living with HIV. They are linked to HIV care and support services.
- All participants receive the best available prevention services, including HIV counseling, free condoms, diagnosis and treatment of sexually transmitted infections, and counseling about other effective prevention strategies, like circumcision to prevent HIV infection in men. It is important to know if PrEP works *above and beyond best HIV prevention services*.

16. Will participants have more risky sexual behaviours because of PrEP?

Concerns about behaviour changes have been raised for other studies of HIV prevention strategies; however, most studies find that research study participants actually reduce their risky sexual behaviours, largely because of the intensive, regular counselling that is part of the research study. At every visit, all participants receive counseling:

- about the importance of adhering to the study procedures,
- that no strategy is 100% effective so multiple strategies must be used,
- that we don't know if PrEP truly reduces the chances of getting HIV, and
- that some participants are taking a placebo instead of PrEP.

Safety in the Partners PrEP Study

17. What happens if participants experience side effects?

At every visit, participants are asked about possible side effects from the medications. Blood tests are also done every three months to assess if PrEP has any effects on kidney or liver function, or on blood counts. Participants who experience side effects receive medical care at the study site or are referred for more specialized care at local health facilities. Treatment for side effects due to the study medication are given free of charge to study participants.

18. How could a participant in the study get HIV?

HIV discordant couples are the largest risk group for HIV infection in Africa, accounting for over 60% of new infections. Participants are given the best quality of proven HIV prevention services, including free condoms, individual and couples counseling. As male circumcision becomes national policy, participants are given information and referrals for available resources. However, in spite of being counseled to use condoms in addition to the study medication, there may be some who do not use condoms consistently and correctly and may become infected with HIV.

19. What happens if a participant becomes infected with HIV?

HIV uninfected participants are tested every month for HIV. Participants who get HIV are counselled and helped to cope with the reality of living with HIV. Blood tests are done at regular intervals to monitor their health and to study how the immune system deals with HIV infection. If a participant who gets HIV during the study needs anti-retroviral therapy, that participant will be provided anti-retroviral therapy either by the study or through referral to a collaborating HIV care program.

20. Is there a risk that people who take the study medicines will develop a resistance to these medications?

HIV drug resistance is the ability of HIV to change and reproduce itself even with anti-HIV drugs in the bloodstream. Drug resistance can make HIV harder to treat.

One of the key questions for studies of PrEP is whether individuals who get HIV while using PrEP will have HIV that is resistant to the PrEP medications. PrEP studies done in monkeys have found that resistance is uncommon in animals that become infected while taking PrEP. In a large phase III study of oral PrEP among 2499 men who have sex with men, 36 men using combination emtricitabine/tenofovir acquired HIV. None acquired HIV that was resistant to emtricitabine or tenofovir using standard HIV-1 genotyping analysis.

For the Partners PrEP Study, several safeguards are in place to minimize the risk of resistance in participants who might become infected even though they have been taking the study medication. First, HIV testing occurs every month for participants taking the study medication, and the medication will be stopped immediately if someone becomes infected. Second, all individuals who get HIV during the study have their virus tested for resistance. This information is provided to the participant and their health care providers, so that HIV treatment, when needed, appropriately takes into account any possible resistance.

21. What care will HIV infected participants receive?

HIV uninfected individuals are taking the study medication and are followed closely in the Partners PrEP Study; however, because the study is among HIV discordant couples, HIV infected individuals are also study participants. Only HIV infected partners who did not meet national guidelines for anti-retroviral therapy at the time of enrollment were eligible for the study. Those who later meet national anti-retroviral therapy guidelines are referred for care and treatment.

The HIV infected participants do not receive study medication. They are seen every three months to monitor their health. Treatment may be provided for other illnesses that they have. If they require anti-retroviral therapy during the course of the study, according national anti-retroviral therapy guidelines, they are offered treatment. Starting anti-retroviral therapy during the study does not affect study participation, and they continue to take part in the study. All study sites either provide anti-retroviral therapy on-site or have close partnerships with HIV care programs providing anti-retroviral therapy.

22. What happens if a female study participant becomes pregnant?

Tenofovir and combination emtricitabine/tenofovir have been used safely by HIV-infected pregnant women, and animal studies have shown that these medications do not harm the developing fetus. However, there is very little experience with these drugs to know about the safety of using them in HIV uninfected pregnant women. As a result, family planning services are provided for all participants. For this study, women taking the study tablets have pregnancy testing at every monthly visit, so that pregnancy can be detected early. If a woman taking study tablets becomes pregnant, the study medication will be stopped but she remains in the study.

Women receive antenatal care. After birth, as part of the study, babies born to women who were taking the study medication at the time they became pregnant are followed for their first year of life, to gather more information on the safety of PrEP when used by women who become pregnant.

23. How will the study make sure participants are not sharing with their HIV infected partner or selling the drugs?

Study drugs are only dispensed to eligible participants in limited quantities (one month supply) at their monthly visit. Participants are counselled at these monthly visits about the importance of adhering to the study procedures and the dangers of sharing the study drugs with any other individuals, including their HIV infected partner.

24. Will participants provide informed consent?

Written informed consent was obtained from each study participant prior to screening and enrollment using forms translated into local languages. Community outreach workers and counselors provide ongoing education to participants about the study procedures and risks and benefits. Participants are under no obligation to continue with the study and may leave at any time.

25. How is the safety and confidentiality of participants maintained?

Confidentiality of participants is of utmost importance. For the Partners PrEP Study, participant data and specimens are identified only by numbers – **no names** are used. Participant files are safely kept in locked cabinets. The information from the study is completely confidential – the study staff does not share the information with anyone.

The Partners PrEP Study Data and Safety Monitoring Board (DSMB) meets every six months to monitor the safety of participants and review the progress of the study. The DSMB is an independent panel of HIV experts, including leading scientists from Kenya and Uganda.

In addition, each study site has at least one Ethics Review Committee (ERC), which approves all research carried out by the study site. They are responsible for assuring the protection of the volunteers who are participating in the study. The ERCs review the study protocol and procedures in detail prior to the study starting and monitor the safety of study participants during the course of the study.