

## **iPrEx: Results of a study of TRUVADA® to prevent HIV infection among MSM**

### **1. What is PrEP?**

PrEP stands for Pre-Exposure Prophylaxis, an experimental approach to HIV prevention where HIV negative people take HIV drugs to try to prevent HIV infection. PrEP is started *before* being exposed to HIV and continued during periods of risk. This is different from post-exposure prophylaxis (PEP) where the medication is started soon *after* exposure to HIV and continued for 28 days. PrEP can be in the form of a pill taken by mouth or a gel applied in the vagina or rectum. Current studies of oral PrEP (pills) have tested the HIV drug tenofovir (also known as Viread®) alone or in combination with emtricitabine (the combined drug is also known as Truvada®) as a daily pill. Both tenofovir and Truvada® are approved for the treatment of HIV infection in HIV- positive people. Preventing an infection by giving a drug that is also used to treat that infection has been a successful approach against other diseases such as malaria.

### **1. What is the iPrEx study?**

iPrEx was a phase 3 study conducted at 11 sites in six countries: in Lima, Peru; Iquitos, Peru, Guayaquil, Ecuador; Boston and San Francisco in the United States; Cape Town, South Africa; Rio de Janeiro and Sao Paulo, Brazil and in Chiang Mai, Thailand. It enrolled 2,499 HIV-negative gay men, male to female transgendered women and other men who have sex with men (MSM).

The main objective of the study was to determine whether tenofovir/emtricitabine (FTC/TDF), a drug that is already being used to treat people living with HIV infection may also help prevent HIV infection in men who are HIV-negative. You may have heard of this drug by its other name, TRUVADA®. In addition to studying whether Truvada® can prevent HIV infection, iPrEx looked at the safety of HIV negative people taking Truvada® daily. The study was looking for any side effects of the drug, along with whether people taking the drug changed their sexual risk behavior. The study was also measuring how well study participants were able to take a daily pill.

The study was funded by the National Institute of Health; additional funding was provided by the Bill & Melinda Gates Foundation. The company that manufactures tenofovir/emtricitabine, Gilead Sciences, is donating the study drug but did not providing funding for the trial.

### **2. What was the study design?**

Participants were randomized to take either the study drug or placebo (sugar pill), EVERY DAY – one pill a day for the duration of the study. They were also counseled about using condoms, got tested for HIV EVERY MONTH, got tested for other STDs every 3 MONTHS, and received risk reduction counseling every visit. Participants were followed for an average of 1.6 years. During their monthly visits, participants were asked about side effects.

### **3. What are the results of the study?**

Individuals who participated in the study were mostly from South America (over 70% of study population was from South America) and at high risk of HIV. At their first visit, the participants reported, on average, having about 18 partners in the last 3 months, and about half of them (53%) reported having more than 5 drinks/day. Participants were coming to the clinic every month for HIV testing and counseling and they were encouraged and reminded to take the study drug every day. Information about adherence (how many pills were missed) was collected in this study.

Unfortunately, despite giving all participants comprehensive HIV prevention services, one hundred (100) HIV infections occurred among 2,499 participants during the study. Of these, 36 infections occurred in the study group that received Truvada<sup>®</sup>, while 64 occurred in the group that received placebo. This means that the rate of HIV infection was 44% lower in men who were receiving Truvada<sup>®</sup> as PrEP. This is a statistically significant level of efficacy, meaning it is highly unlikely these results are due to chance. It should be emphasized that it was very important to take the medication and to be monitored for HIV infection as well as receive comprehensive evaluations for any side effects.

### **4. What does 44%, or partially effective mean?**

First, 44% is just an estimate of how much being given Truvada<sup>®</sup> reduced the risk of HIV infection. The 95% confidence intervals (95% CI) for this study was 15% - 63%, meaning that it can be determined with 95% confidence that the true efficacy in this trial falls somewhere between 15 and 63%.

These results apply to the overall population of participants being given Truvada<sup>®</sup> compared to placebo, not to individual people. So, it is not accurate to say that one person taking PrEP has a 44% less chance of becoming HIV infected than a person who is not taking PrEP. Rather, among the 2,499 participants enrolled in this study, those in the group given PrEP were 44% less likely to become HIV infected than those in the group given the placebo.

What this protection means for HIV prevention in general or for individual people will require further analyses of these data, in addition to further studies of participants' ability to take the pills, how best to provide them in the context of other HIV prevention services, and other considerations.

### **5. Was PrEP more effective when people took the pill more consistently?**

It should be emphasized that it was very important to take the medication and to be monitored for HIV infection as well as receive comprehensive evaluations for any side effects.

Many study participants found it challenging to take the study pills on a daily basis. The data also shows, however, that those participants who were able to take the pill more often may have been more likely to be protected from HIV infection than those who took the pills less frequently. It should be noted that measuring pill taking can be challenging – pill taking in this study was recorded in 4 different ways. None of these measures is perfect, and in this and

other studies, we often find that the information we get from different measures of pill taking don't agree with each other. There are likely many reasons for this including people not remembering exactly how many pills they take; losing, forgetting, or discarding pills; and differences in how much study drug is absorbed into the blood.

Even understanding these limitations, participants who reported taking the drug more often experienced more protection:

- Study participants who reported taking Truvada® on 50% or more of days had 50% fewer HIV infections (95% CI 18-70%; P=0.006).

- Those who reported using PrEP on 90% or more of the days had 73% fewer HIV infections (95% CI 41-88%; P=0.001).

In this study, blood levels of study drug were compared in 34 people who became HIV infected and a matching group of 43 people who remained HIV-negative. Among those given Truvada®, study drug was detected in less than 10% of people who became HIV infected and about half of those who remained HIV-negative. This finding suggests that participants who had drug detected in their blood were more likely to be protected from HIV than those who didn't. It is important to realize that samples were only tested in a small number of people and at only one snapshot in time. Therefore, drug level testing in many more samples is being planned for this study.

Further studies will also be required to understand how to help people take the pills more consistently, and to what extent doing so will increase protection against HIV.

## 6. Were there any side effects or risks to taking the medication?

Overall, the study drug was well tolerated. Below is a brief summary of key side effects noted in the study.

**Nausea:** In the early few weeks of the study, participants who took the study drug experienced more nausea than individuals who took the placebo.

**Kidney function:** There were a few mild abnormalities in kidney function (inflammation of the kidney is often seen in HIV infected patients who take Truvada® as part of their regimen – it often goes away after the medication is stopped). 2% in the group receiving Truvada® vs. 1.1% in the placebo group experienced increase in creatinine (which marks kidney function). But there were not significant differences in kidney function between the group that took the drug and the group that took the placebo. None of the abnormalities were permanent (they resolved after the medication was stopped).

**Unintentional weight loss:** unintentional weight loss of more than 5% was reported in 2.2% of people receiving PrEP compared with 1.1% of placebo users (P=0.04).

These side effects mirror those found in previous PrEP studies conducted by Family Health International among women in West Africa and by the U.S. CDC among MSM in the United States. They are also consistent with the experience of HIV-positive people taking Truvada® for treatment of HIV infection.

Because it appears that many participants may not have been taking a daily pill throughout the study, and because participants were seen in the study only for an average of one year, these estimates of side effects may not reflect what would be seen if the pill is taken daily or for a longer period of time. More information on the safety of Truvada® will come from additional data from iPrEx and from other studies in the field.

## 7. Did taking PrEP lead to drug resistance in this study?

One of the concerns we always have is whether or not taking this medication can lead to development of resistance, especially since it is taken by individuals who are HIV negative and are getting exposed to the HIV virus. That is why getting tested for HIV frequently was very important: so that individuals who got infected stopped PrEP and were referred for care and evaluation. We know that taking only two drugs if someone is HIV-infected is not a good idea because the virus can mutate (change) and develop resistance to the drugs.

In the study there was little drug resistance. Two cases of resistance to the emtricitabine component of Truvada® occurred. When resistance occurred, it developed in a two people who took Truvada® and were infected right at enrollment, but their infection was too recent to be detected by HIV antibody tests at enrollment. They were found to be HIV antibody positive at their next visit, one month later. Stored blood specimens from their enrollment visit were found to have HIV present by viral load testing.

While many effective treatments remain available for people with emtricitabine resistance, it will still be important, if PrEP is made widely available, to do everything possible to minimize the chances of drug resistance for anyone using PrEP.

In order to minimize the chance for resistance, it will be important to ensure regular HIV testing of anyone using PrEP, and to stop PrEP immediately if a person becomes HIV infected. Additionally, PrEP providers would need to perform both HIV testing and a health screen for viral symptoms before starting a patient on PrEP, to decrease the chances of giving PrEP to someone already HIV infected.

## 8. What are take home points?

**Truvada®, when taken consistently once a day in combination with condom use, risk reduction counseling and STD care, and monthly HIV testing, decreased the risk of HIV infection by 44% among MSM.** In this study, participants were encouraged to take the medications on an ongoing basis that is not tied to specific behavior or possible exposure. These results are exciting since they expand the prevention toolbox for MSM; this drug should be used in addition to other interventions (condoms, testing) and should be coordinated under the care of a health professional.

There are other studies that are evaluating oral PrEP in other populations such as IVDU (Thailand), women, serodiscordant heterosexual couples, as well as looking at intermittent PrEP taken less frequently. We don't have the results of these studies yet.

## **9. What is the significance of these results?**

The iPrEx study is a clear and important step forward for HIV prevention research. These results mean that PrEP may be an additional tool for HIV prevention for MSM and transgender women when used in combination with standard HIV prevention tools such as HIV testing and counseling, provision of condoms and lube, and STI testing and treatment. Besides being the first study to report on and demonstrate the efficacy of oral PrEP in people, iPrEx is the first randomized clinical trial to demonstrate a protective effect for a biomedical intervention against HIV in MSM. These data address an important unmet need in public health, as HIV infection rates are higher in MSM than among other groups in almost all countries. It is unknown how a partially effective intervention such as PrEP might be best used. For MSM who cannot consistently use condoms however -- especially those living in settings with high rates of HIV -- even a partially protective intervention such as PrEP might be beneficial.

## **10. What are some remaining questions?**

- Whether PrEP is safe and effective in populations other than MSM and transgender women who have sex with men
- The safety and potential protective effect of alternative dosing regimens, (e.g., intermittent PrEP). Additional studies are planned to look at whether intermittent PrEP (e.g. taking PrEP either before and after sex, or on a regular schedule several times a week) can be safely taken.
- How to best implement a PrEP program or the cost-benefit of doing so
- The potential public health impact of providing broad access to PrEP for HIV prevention
- The patterns of risk behavior and pill taking that may occur now that more information is available about PrEP safety and efficacy