



UNIVERSITY OF WASHINGTON  
INTERNATIONAL CLINICAL RESEARCH CENTER  
PARTNERS PrEP STUDY

## THE RESULTS OF iPrEx

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### **SUMMARY**

On 23 November 2010, the results of iPrEx, a randomized, placebo-controlled, clinical trial of a combination oral emtricitabine/tenofovir pre-exposure prophylaxis for the prevention of HIV infection in men who have sex with men, were published in the *New England Journal of Medicine*.

iPrEx is the first efficacy study to test whether oral pre-exposure prophylaxis (or PrEP) can prevent HIV infection. With PrEP, an HIV uninfected person uses an antiretroviral (ARV) medication to reduce the chances of getting HIV. PrEP is currently being studied using oral ARV-containing tablets and vaginal ARV-containing gels.

iPrEx provides clear evidence that PrEP might be able to be safely used for HIV prevention. The results of iPrEx are an important milestone in HIV prevention. More research is needed to confirm these results in other populations and to test whether other ARV-based prevention strategies can be even more effective for preventing HIV. Ongoing ARV-based prevention trials, including the Partners PrEP Study, are testing whether PrEP is safe and effective for HIV prevention in populations in Africa.

**iPrEx is an important HIV prevention trial. This study has demonstrated that an oral ARV (a pill containing the combination emtricitabine/tenofovir) reduces the risk of becoming HIV infected for men who have sex with men. The study was conducted with high quality, and it provides a critical “proof of concept” in the path to using ARV medications for HIV prevention.**

### **WHAT IS iPrEx?**

- iPrEx was a phase III clinical trial to assess the safety and efficacy of oral PrEP for the prevention of HIV infection, using a combination ARV-containing tablet with the medications emtricitabine and tenofovir in a single tablet (also called Truvada)
- The study population for iPrEx was men who have sex with men. The study was designed to assess if oral emtricitabine/tenofovir PrEP could reduce HIV risk by 60%.
- The study was funded by the US National Institutes of Health and the Bill & Melinda Gates Foundation. Study drug was donated by Gilead Sciences, Inc.

- In total, 2499 men who have sex with men were enrolled at 11 study sites in 6 countries: Peru (Lima and Iquitos), Ecuador (Guayaquil), Brazil (Rio de Janeiro and Sao Paulo), the United States (Boston and San Francisco), South Africa (Cape Town) and Thailand (Chiang Mai). The majority were from the Peru and Ecuador sites; less than 5% each were from the South Africa and Thailand sites.
- iPrEx study participants were randomly assigned, in an equal number, to one of two study groups: one group received pills containing emtricitabine/tenofovir and one received tablets containing placebo, each to be taken orally once a day.
- Prior studies have shown that oral tenofovir and combination emtricitabine/tenofovir are well-tolerated and safe when used daily by HIV uninfected for men and women. In July 2010, a large 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 for extended use. That study was not designed to be large enough to measure whether tenofovir prevented HIV.
- All participants received intensive HIV risk-reduction counseling, free condoms, and other HIV prevention services. The trial started in June 2007, enrollment was completed in December 2009, and the primary analysis included participant follow-up through May 1, 2010.

### **WHAT DID iPrEx FIND?**

- The study found that oral emtricitabine/tenofovir PrEP was safe.
  - There were no statistically significant differences in the rate of serious adverse events or laboratory adverse events between participants who received active PrEP and those who received placebo.
  - Abnormal creatinine levels in blood were found in 2% (=25 participants) of those receiving PrEP and 1% of those receiving placebo (=14 participants) – this difference was not statistically significant. Of the 25 participants from the active PrEP arm who had an abnormal creatinine value during the study, only 5 had abnormal results that confirmed on repeat testing. All resolved with temporary discontinuation of PrEP, and 4 participants successfully restarted on PrEP without abnormal results afterwards.
  - There were small differences in the frequency of nausea (2% vs. <1% of participants) and weight loss (2% vs. 1% of participants) between the active and placebo arms. Most of the difference in nausea frequency was present early in the study and resolved after the first few weeks of taking the study medication.
- The study found that oral emtricitabine/tenofovir PrEP was effective for preventing HIV.

- iPrEx found that there were 44 percent fewer HIV infections in men assigned to the emtricitabine/tenofovir arm compared to men assigned to the placebo arm. During the study, 36 men in the emtricitabine/tenofovir arm acquired HIV, compared with 64 men in the placebo arm.
- The result of 44 percent effectiveness of oral emtricitabine/tenofovir was statistically significant, although the confidence interval of the result, which defines a range of reliability for the study finding, found that the true effectiveness of emtricitabine/tenofovir in iPrEx could be as low as 15 percent or as high as 63 percent.
- In subgroup analyses from the trial, oral emtricitabine/tenofovir PrEP had greater benefit for protection against HIV infection if adherence was high ( $\geq 90\%$  estimated pill use). In the group with  $\geq 90\%$  estimated pill use, the effectiveness of emtricitabine/tenofovir was 73%.
- In a small group of participants who did not acquire HIV, blood levels of emtricitabine and tenofovir were checked – only about half had any detectable levels. In those who did acquire HIV, only  $\sim 10\%$  had any emtricitabine or tenofovir in their blood. Thus, the efficacy results may have been influenced by less than optimal adherence to the daily PrEP medication.
- Among the 36 men in the emtricitabine/tenofovir arm who acquired HIV, none had HIV that was resistant to emtricitabine or tenofovir detected by standard HIV genotyping analysis.
  - However, an additional 2 men who were already infected with HIV at the time of study enrollment, but whose HIV antibody tests were negative (thus, who were in the “window period” of HIV infection), and who were assigned to the emtricitabine/tenofovir arm, developed resistance to emtricitabine. They did not develop tenofovir resistance.
- High-risk sexual behavior declined during the study, in both the active and placebo arms.

## **WHAT DOES iPrEx TELL US?**

- iPrEx was designed to determine whether men who have sex with men who are at risk of HIV can be safely protected against infection using a daily oral combination emtricitabine/tenofovir tablets. As such, the study’s findings provide information about the emtricitabine/tenofovir tablets when used in this particular manner and for this particular population. iPrEx is the first study to demonstrate the effectiveness of an oral daily antiretroviral (ARV) for HIV prevention. In addition, iPrEx demonstrated that PrEP was safe for daily use. The results are extremely encouraging for the PrEP field.

- We already know medicines called antiretrovirals, or ARVs, are effective for treating people who are already infected with HIV. We believe they also have great potential for preventing HIV.
  - The results of iPrEx build on the findings of CAPRISA 004, which found that tenofovir vaginal gel reduced HIV risk in women. Together they show that PrEP – as tablets and as a topical vaginal gel – has great promise.
  - While we are excited about these results, more information is needed before we will know whether tenofovir (in a tablet or a gel) can prevent HIV in other settings and in other populations. Policymakers and regulators will require clear and compelling evidence for HIV prevention and safety to implement PrEP in their populations.
- Now, more than ever, research on PrEP in populations with different types of HIV exposure, risk factors and adherence is required. Because the study involved only men who have sex with men, most from South America, PrEP might work differently in heterosexual populations (in which the risk of HIV transmission with each sex act is substantially lower than for sex between men) and in populations where adherence to the study medication may be higher. That is why evaluation of any new intervention almost always requires more than one study – often several – to gain as much information as possible about its safety and effectiveness in different populations who could potentially benefit.
  - Ongoing PrEP studies involving women and heterosexual men from Africa could feasibly tell a different story about the efficacy of PrEP than what is found in iPrEx. Different routes of HIV exposure, differences by gender, different adherence, and different geographic locations for the ongoing PrEP studies could mean very different results – either more or less protective against HIV, more or less safe and tolerable – compared with iPrEx. Differences in the relative frequency of HIV exposure (particularly number of sexual partners), risk of HIV transmission (for anal versus vaginal sex), presence of other cofactors that increase HIV risk (like rates of male circumcision and sexually transmitted infections), and adherence to study drug are likely to be substantial between the iPrEx population and the heterosexual African populations participating in other PrEP studies.
  - iPrEx is one of six ongoing or completed, placebo-controlled, efficacy trials of PrEP. Five of these trials are evaluating oral tenofovir or emtricitabine/tenofovir tablets as PrEP, and two trials are evaluating tenofovir gel [see table below]. The gel studies are commonly thought of as microbicide studies; however, the concepts of using tenofovir as a gel or as a tablet for HIV prevention are similar in many ways.
  - There are important differences between the studies: different geographic locations of the study populations, different route of HIV exposure (man-to-man, woman-to-man, man-to-woman, and via injection drug use), as well as the potential for different side effects, adherence, and acceptability. All of these may have an impact on the efficacy of PrEP for preventing HIV.

- Each of the ongoing studies evaluating PrEP is critical for advancing understanding about the safety and effectiveness of this strategy among different populations. Results from one study will not necessarily predict the results for other studies, because of the important differences in population, frequency and route of HIV exposure, and potential for different adherence.

<b>EFFICACY STUDIES OF ORAL AND TOPICAL TENOFOVIR FOR HIV PREVENTION, NOVEMBER 2010</b>				
<b>Location</b>	<b>Sponsor/ Funder</b>	<b>Population</b>	<b>Agent</b>	<b>Status</b>
Thailand <i>Bangkok Tenofovir Study</i>	CDC	2400 IDU	Oral tenofovir	Fully enrolled <b>Results potentially 2011</b>
South Africa <i>CAPRISA 004</i>	CAPRISA / USAID	900 women	Vaginal tenofovir gel (coital use)	Completed <b>Vaginal tenofovir gel reduced HIV risk by 39% (95% CI 6-60%, p=0.02)</b>
Brazil, Ecuador, Peru, S. Africa, Thailand, US <i>iPrEX</i>	UCSF/ NIH& BMGF	2499 MSM	Oral emtricitabine/tenofovir	Completed <b>Results November 2010</b>
Kenya, Uganda <i>Partners PrEP Study</i>	UW / BMGF	4700 HIV discordant couples	Oral tenofovir, Oral emtricitabine/tenofovir	Fully enrolled Results late 2012
Kenya, South Africa, Tanzania <i>FEM-PrEP</i>	FHI / USAID& BMGF	3900 high- risk women	Oral emtricitabine/tenofovir	Enrolling Results 2013
South Africa, Uganda, Zimbabwe <i>VOICE / MTN 003</i>	MTN / NIH	5000 women	Oral tenofovir, Oral emtricitabine/tenofovir, Vaginal tenofovir gel (daily use)	Enrolling Results 2013

- No single trial can provide all of the answers. We need more research to confirm these findings, including studies in heterosexual populations. HIV discordant couples are a priority population for understanding the relative efficacy and cost-effectiveness of treating the HIV-infected partner with ART compared to providing the HIV-uninfected partner with PrEP.
- The Partners PrEP Study is a unique study and one that we feel will provide important information for women and men at risk of HIV.
  - iPrEx found that combination oral emtricitabine/tenofovir reduced the risk of HIV infection among men who have sex with men. We do not know from whether oral tenofovir-based PrEP will be safe and effective for preventing HIV for heterosexual men and women from Africa.
  - The Partners PrEP Study has implemented multiple strategies to maximize and accurately measure adherence to PrEP.
  - The Partners PrEP Study is the only study evaluating PrEP in HIV serodiscordant couples, who are a priority population for HIV prevention, particularly in Africa, and are likely to be motivated to take up prevention strategies with high adherence. It is the only PrEP study that includes heterosexual men.

- We're very happy and encouraged about the results of iPrEx – the study provides strong initial evidence that PrEP can prevent HIV. The iPrEx Study also demonstrates the importance of targeting populations who are at high risk of HIV infection and are able to take the tablets with high adherence.
- Active and meaningful engagement in research includes timely communication when there is new information of potential interest or concern. The teams at each Partners PrEP Study research site understand the importance of building and maintaining relationships of trust with study participants, their partners and members of the community. As part of this commitment, study teams will inform their Institutional Review Boards (IRBs) and talk with participants about iPrEx and what the results mean for the Partners PrEP Study.