

QUESTIONS AND ANSWERS: *US CDC PrEP Safety Study and CAPRISA 004*

1. What is PrEP?

PrEP stands for Pre-Exposure Prophylaxis, an approach to HIV prevention that is currently being tested where people at risk for HIV take HIV drugs to try to prevent HIV infection. PrEP is started before being exposed to HIV and continued during periods of risk, which is different from post-exposure prophylaxis (PEP) where the medication is started soon after exposure to HIV and continued for 28 days only. 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 are testing the HIV drug tenofovir (also known as Viread) alone or in combination with emtricitabine (the combined drug is also known as Truvada). Both tenofovir and Truvada are approved for the treatment of HIV infection in HIV-positive people.

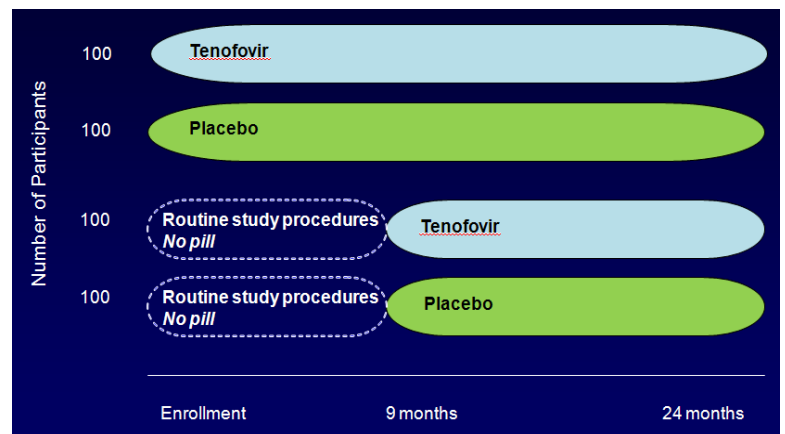
2. What is a microbicide?

Microbicides are substances, like creams or gels, that are used vaginally or rectally to try to prevent HIV infection, and possibly other sexually transmitted infections and/or pregnancy. Several microbicides are currently being tested, some of which contain HIV drugs, such as tenofovir. Currently, there are no approved microbicides or PrEP pill regimens that have been demonstrated to prevent HIV infection.

3. What was Project T testing?

Project T was testing the long-term safety of the tenofovir pill, a common HIV drug, in HIV-negative men who have sex with men (MSM). Project T tested safety both in terms of the physical side effects of the drug, as well as whether taking a daily pill might affect HIV risk-taking behavior. The study was not designed to test whether tenofovir prevents HIV infection.

In order to measure whether taking a pill impacts risk behavior, Project T featured a unique study design where half the study participants started taking pills right away (either tenofovir or placebo, a dummy pill), and the other half started pills nine months after they enrolled in the study (either tenofovir or placebo) (see diagram to the right). In this way, researchers could compare the risk-taking behaviors of the groups to see whether taking the pill was associated with a change in risk behavior.



Project T focused on MSM because of the high rates of new HIV infections in this group in the U.S. and many other countries. Other studies were already testing PrEP in other groups at risk for HIV, including heterosexual women and injection drug users.

Project T was sponsored by the Centers for Disease Control and Prevention (CDC). In collaboration with the San Francisco Department of Public Health, AIDS Research Consortium of Atlanta, and the Fenway Community Health Clinic, 400 men were recruited in San Francisco, Atlanta and Boston. This study enrolled participants between February 2005 and July 2007 and followed participants for 2 years.

4. What are the results for Project T/US CDC Safety study?

In preliminary analyses, we found no significant medical safety concerns with taking a daily tenofovir pill in HIV-negative men who have sex with men (MSM) in this study. Also, men did not take more risks sexually while taking a pill in this trial. It is important to note that participants knew they had a 50/50 chance of getting a placebo (dummy pill) and were also counseled that it is not known whether tenofovir is effective in preventing HIV. Therefore, these findings may not reflect what will happen with risk behavior outside of a study, especially if tenofovir is found to be effective in preventing HIV. Additional analyses are being performed to look at other medical safety and risk behavior measures, as well as levels of pill-taking in the study. These results will be announced at a later date.

4a. Did any HIV infections occur among participants in the US CDC Safety Study?

Unfortunately, several men did become HIV-positive while in this study. Three of the HIV infections occurred among participants while taking the daily pill. All 3 of these men were taking the placebo tablet. No conclusions about whether tenofovir can prevent HIV infection can be drawn from this study, as it was not designed to test the effectiveness of PrEP. Much larger studies are ongoing around the world to try to answer this question.

5. What was CAPRISA 004 testing?

CAPRISA 004 was testing the safety and effectiveness of 1% tenofovir gel (a type of microbicide) in preventing HIV infection in 889 HIV-negative women in South Africa. Half of the women in the study received tenofovir gel, while the other half received a placebo gel (no active ingredient). Neither researchers nor participants knew an individual's gel assignment. Women were advised to apply the gel vaginally up to 12 hours before sex and as soon as possible but within 12 hours after having sex.

CAPRISA 004 focused on women at high risk for infection. In Africa, about 60 percent of new HIV infections are acquired by women and girls. Correct and consistent use of male condoms has been shown to prevent HIV infection, but women are often unable to negotiate condom use with their male partners.

This study was sponsored by the United States Agency for International Development (USAID), Family Health International and the South African Department of Science and Technology.

6. What are the results for CAPRISA 004?

This study showed that there were 39% fewer infections in women who received 1% tenofovir gel compared with women who received a placebo gel (no active ingredient). This study also found that the tenofovir gel was 51% effective in preventing genital herpes infections among women who tested negative for herpes when they joined the study. Women who reported higher use of the gel had a greater protective effect against HIV and genital herpes. There were no significant safety concerns from use of the gel in this study. Also, no increase in risky behavior was observed in women in the study. Women were provided risk reduction counseling, condoms, and treatment for sexually transmitted infections during the trial.

7. How are these studies related to one another?

Although both the US CDC Safety Study and CAPRISA 004 tested tenofovir as a potential strategy for HIV prevention, there are a number of differences between these studies. These differences include the types of people studied, the product being tested, how this product was taken, as well as the goals of the study. These distinctions are described in the table below.

	US CDC Safety study	CAPRISA 004
Population studied	Men who have sex with men	Women
Location	United States	South Africa
Product tested	Tenofovir pill	Tenofovir gel
How was it used?	Taken by mouth	Inserted into the vagina
When was it taken?	Daily	Before and after sex
Main question study addressed	Is tenofovir pill safe?	Is tenofovir gel safe and effective for HIV prevention?

8. What do these results mean for San Francisco?

The initial results from the Project T study provide important information on the safety of daily oral tenofovir in men who have sex with men (MSM) in the United States. However, we still need to know whether oral PrEP is effective for HIV prevention before it could be recommended for use in San Francisco. The San Francisco Department of Public Health is currently testing whether PrEP using Truvada (tenofovir + emtricitabine combination pill) is both safe and effective in preventing HIV as part of a large global study among MSM called iPrEx (also known as PREPARE in San Francisco); results from this study will be available in early 2011.

Results from the CAPRISA 004 study provide important data on the safety and effectiveness of vaginal tenofovir gel in women in Africa, but are only a first step in determining whether this gel can be used for HIV prevention. Additional studies are needed to confirm and extend these findings. The VOICE study, which is testing tenofovir gel used on a *daily* basis as well as tenofovir and Truvada in pill form, is currently enrolling women in several African countries and will likely have results in the next few years. We do not know whether tenofovir gel (which is different from the tenofovir pill) will protect men who have sex with men (MSM), the group at highest risk for HIV in the United States. The safety and effectiveness of using the gel rectally is not known. Further studies are needed to determine whether tenofovir gel is safe and effective for preventing HIV transmission during anal sex.

9. How was the community involved in Project T?

The HIV Research Section in the SF Department of Public Health (SFDPH) is committed to conducting innovative research in collaboration with communities most affected by HIV. Project T was conceived of and developed in close collaboration with the SFDPH Community Advisory Group, a group of community members who provide input into all levels of research being conducted by the SFDPH HIV Research Section. In fact, the

delayed treatment arm of the study to test how pill-taking might affect risk behavior was developed as a result of this community group's advice.

In addition, the SFPDPH held several community consultations and educational forums in San Francisco to gain further feedback and educate the community about Project T before the study began, and continued to actively offer educational workshops and forums throughout the course of the study. SFPDPH also partnered with community based organizations for recruitment into the study, and plans to do so to share results of the study broadly.

10. Did we learn anything about rectal use in CAPRISA?

a. What rectal microbicides are being tested?

b. Can vaginal microbicides be used rectally?

The CAPRISA 004 study tested tenofovir gel for vaginal use in African women. Therefore, the safety and effectiveness of using this gel rectally is not known. Given that the anatomy and functions of the rectum are different from the vagina, it is likely that the side effects and effectiveness of this and other microbicides may differ when used rectally.

Several preliminary studies are being planned or underway to evaluate the safety of different rectal microbicides. Current efforts are underway to adapt the formulation of tenofovir gel for rectal use. If these products appear to be safe when used rectally, they will be tested to see if they are effective for HIV prevention in larger studies. For more information about rectal microbicide studies, please visit www.global-campaign.org/rectal.htm.

11. Can oral pills be used to make tenofovir gel?

No. Tenofovir gel is made through a complex process under strict manufacturing conditions and is not derived from oral pills.

12. How was participant safety protected in the studies?

The safety of study participants is of utmost concern in any research study. Before joining the study, all Project T study participants went through an extensive informed consent process where they learned in detail about the study, including all the risks and benefits of taking part, and that they could leave the study at any time. That process included understanding and signing a written informed consent document, as well as multiple one-on-one meetings with counselors and study staff to answer any questions. After enrolling in the study, participants had access to a study clinician at all times to address any questions or concerns they might have.

All participants received regular HIV testing and risk reduction counseling as well as condoms and lube during the study. Participants recruited into this study were at risk for HIV, and a few became HIV positive during their participation. At that point, study staff provided linkages to appropriate care for their mental and physical health and well-being, including antiretroviral treatment. Those participants were also asked to stop taking the study drug, but to continue coming in for visits for another six months. The study medication itself did not contain HIV virus and could not cause HIV infection.

In addition to multiple community consultations, Project T was reviewed and approved by institutional review boards in each of the study cities, who considered the medical importance of the study and that the study procedures were ethically sound. In addition, a Data and Safety Monitoring Board (DSMB) was formed of investigators not involved in the trial. This group met two times per year throughout the trial to monitor safety data in the trial.

13. If all the people in the studies were encouraged to use condoms, how did you find out if it worked?

Project T was a safety study, so it was not testing whether tenofovir works to prevent HIV infection. As with all HIV prevention studies, Project T participants were provided free condoms and ongoing HIV-risk reduction counseling to help them reduce their risk of HIV while in the study.

In efficacy studies, like CAPRISA 004, all participants were also offered risk reduction counseling and provided with condoms to help them reduce their risk, because it is unknown whether the microbicide works to prevent infection, and participants may be receiving a placebo, which offers no protection. Though these measures often work to reduce HIV-risk taking behavior, most participants are not able to use condoms 100 percent of the time. At the end of the study, researchers compared the group who got the tenofovir gel with the group who received placebo to see whether the tenofovir gel lowered the rate of becoming infected with HIV.

14. What are the next steps for PrEP research?

- a. What additional analyses will emerge from these studies?**
- b. What will further PrEP studies tell us?**
- c. What other medications are being studied for PrEP?**

Additional analyses are being conducted in the Project T study, and these results will be announced at a later date. These analyses will look at additional medical safety and risk behavior measures as well as levels and patterns of pill-taking in the study. However, more safety data in larger groups of people will still be needed to determine the biological safety of PrEP and how to prevent increases in risk behavior if PrEP is shown to be effective.

Several large studies are currently testing the safety and effectiveness of daily oral PrEP around the world. These include studies in injection drug users in Thailand, heterosexual women in Africa, and couples in Africa. iPrEx is a global study testing whether a combination drug Truvada, (tenofovir combined with emtricitabine) is safe and effective for HIV prevention in MSM in 6 different countries. Results from the iPrEx study will be available in 2011. For more information about the iPrEx study, please see globaliprex.net.

Other studies are beginning to look at the safety and ease of pill-taking of different dosing regimens of oral PrEP (e.g. taking PrEP either before and after sex or on a regular schedule several times a week – also known as intermittent PrEP). These studies are taking place in Thailand, Africa, and the United States. Taken together, these studies will help determine if and how best to use PrEP to reduce HIV infections around the world.

The encouraging results for tenofovir gel in the CAPRISA 004 study need to be confirmed. The VOICE study, a study being conducted by the Microbicide Trials Network of the National Institutes of Health, will tell us about the safety and effectiveness of *daily* use of tenofovir gel in women, information that will complement the

CAPRISA 004 study. VOICE will also tell us about the safety and efficacy of daily use of a tenofovir or Truvada pill. This study is currently enrolling and will likely have results in the next few years. Additional studies are currently being planned to test the use of tenofovir gel rectally in different populations, including MSM.

15. What might PrEP use look like in different communities?

How PrEP may ultimately be used is currently unknown, and will be a complex issue determined in part by ongoing PrEP studies. People who might benefit if PrEP is found to be safe and effective include sexually active men who have sex with men (MSM), partners of HIV positive people, commercial sex workers, and couples who want to have a child where one partner is HIV positive. If PrEP is found to be safe and at least partially effective, agencies like the Center for Disease Control and Prevention (CDC) in the United States, or the World Health Organization (WHO) internationally, will consult with a wide variety of experts and relevant community groups to establish guidelines for PrEP use.

Considerations that will be taken into account will include: which populations are most likely to benefit from PrEP, how much it would cost, how effective it is, concerns that it may increase HIV risk-taking behavior, and possible drug resistance if the drug is used for treatment and prevention, as well as how often people should have HIV testing and be monitored with laboratory tests, and many others.

16. Can I take tenofovir to protect myself from HIV?

We don't yet know whether PrEP taken orally is effective for HIV prevention. Therefore, it is not recommended that PrEP be taken at this time. Men in this study were carefully chosen to not have any kidney or other major medical problems. Tenofovir could be harmful if not taken under a doctor's supervision.

Also, because tenofovir gel was only tested for vaginal use in women in Africa, it is not known whether this gel would be effective in other populations, including men who have sex with men who use it rectally. Further studies will be needed to confirm the results in women and evaluate the safety and effectiveness of rectal use of tenofovir gel in men. Tenofovir gel is only available for research studies at the present time.

17. Does PrEP have to be taken every day?

The first round of PrEP studies are testing whether daily dosing of PrEP is safe and effective for HIV prevention. This dosing regimen was selected because it is the same used for HIV treatment; however, at this time, it is not known what the optimal dosing schedule will be, if PrEP is shown to be effective. 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.

18. What will it mean if PrEP is partially effective?

It is very likely that PrEP will not be 100% effective. As a hypothetical example, studies may show that PrEP is 50% effective in preventing HIV. This imaginary finding would mean that PrEP would prevent half of the infections that would have occurred if PrEP wasn't being taken.

Because PrEP is unlikely to be effective all the time, PrEP will need to be combined with other prevention strategies to have the largest benefit. These strategies will include prevention tools we already have (condoms, HIV testing and counseling) as well as new HIV prevention strategies that are being tested.

19. What does it mean that tenofovir gel was found to be 39% effective?

The CAPRISA 004 study found that tenofovir gel was 39% effective in reducing a woman's risk of becoming infected with HIV and 51% effective in preventing genital herpes infections in the women participating in the trial. This means that the tenofovir gel prevented 39% of the HIV infections that would have occurred if the tenofovir gel was not used. Also, the gel prevented approximately half of the genital herpes infections that would have occurred in women who tested negative for herpes at the beginning of the study. It is important to note that in both cases, tenofovir gel reduced – but did not eliminate – each woman's risk of being infected with HIV or genital herpes during the study.

20. Where do I get more information?

For more information about PrEP, please visit the following websites:

Prepwatch website hosted by the AIDS Vaccine Advocacy Coalition (AVAC): www.avac.org/prep

Information about the CAPRISA 004 study results: www.avac.org/CAPRISA004

Center For Disease Control and Prevention (CDC) PrEP website: <http://www.cdc.gov/hiv/prep/index.htm>

IRMA, International Rectal Microbicides Advocates: www.rectalmicrobicides.org

San Francisco Department of Public Health HIV Research Section website: www.helpfighthiv.org

You can also contact our study staff at 415-554-9055 or alfonso.diaz@sfdph.org for more information.