



**CONTACT: Lisa Rossi**  
**+1- 412- 916-3315 (mobile)**  
**rossil@upmc.edu**

**FOR IMMEDIATE RELEASE**

## **Microbicide Trials Network Statement on Decision to Discontinue Use of Tenofovir Gel in VOICE, a Major HIV Prevention Study in Women**

**PITTSBURGH, November 25, 2011** – VOICE, an HIV prevention trial that has been evaluating two antiretroviral (ARV)-based approaches for preventing the sexual transmission of HIV in women – daily use of one of two different ARV tablets or of a vaginal gel – will be dropping the vaginal gel from the study. The decision to discontinue use of the gel, which contains the ARV tenofovir, comes after a routine review of study data concluded that tenofovir gel was not effective in preventing HIV in the women enrolled in the trial.

Importantly, the review, which was conducted by the National Institute of Allergy and Infectious Diseases (NIAID)'s independent Prevention Trials Data and Safety Monitoring Board (DSMB), identified no safety concerns with either tenofovir gel or the oral Truvada® tablet, a combination of tenofovir and emtricitabine. In fact, VOICE will continue to test the safety and effectiveness of Truvada.

The other oral tablet, tenofovir, was discontinued from the study after a routine DSMB review in September determined that although the tenofovir tablets were safe, they were no better than placebo in preventing HIV in the women assigned to that study group.

[VOICE](#) – Vaginal and Oral Interventions to Control the Epidemic – is being conducted at 15 trial sites in Uganda, South Africa and Zimbabwe that had enrolled 5,029 sexually active HIV-negative women. The trial is being conducted by the [Microbicide Trials Network](#) (MTN), an HIV/AIDS clinical trials network funded by NIAID with co-funding from the *Eunice Kennedy Shriver* Institute for Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health.

The study was designed with five study groups: tenofovir gel, an inactive placebo gel, oral tenofovir, oral Truvada and an inactive placebo tablet. The women in each group (about 1,000) were asked to take their assigned study product daily. As designed, the study is intended to determine how each product works compared to its control (placebo gel or placebo tablet) and which approach women prefer. VOICE has been the only trial evaluating the daily use of an ARV tablet – an approach called oral pre-exposure prophylaxis, or PrEP – and a vaginal gel in the same study.

The most recent DSMB review took place Nov. 17 and included study data for the period between Sept. 9, 2009, when the study began, and Sept.30, 2011. Based on this review, the DSMB recommended that VOICE discontinue the tenofovir gel and placebo gel arms, because there was no difference in effect between them in preventing HIV infection. The HIV incidence rates in the two groups were nearly identical, with a 6.1 percent incidence rate in the placebo gel group and 6.0 percent in the tenofovir gel group. HIV incidence represents the number of new infections that occur in a population over a specific period of time. In the case of VOICE, this means that for every 100 women in the gel arms, six acquired HIV in the course of a year.

In light of the strong evidence showing that tenofovir gel did not work in the study's participants, the DSMB recommended that the women randomized to the tenofovir gel and placebo gel groups discontinue their use of the study product and be exited from the study as soon as it would be feasible to do so.

All VOICE participants are being informed about this latest modification to the study. Because the DSMB had no major concerns about the safety of tenofovir gel, the participants randomized to the vaginal gel arms will discontinue use of their assigned study product at their next scheduled clinic visit in December or January. In keeping with the normal process for women ready to exit the study, the women in the two gel groups will return to the study clinic eight weeks after stopping their assigned study product for a last set of tests and procedures,

**-more-**

including HIV testing and counseling. During this last study visit, the participants will be “unblinded” and learn whether they received tenofovir gel or the placebo gel during the study. They will also be provided information about where they can receive HIV testing and counseling, contraception and other medical or support services as needed.

Women who became HIV-infected and/or pregnant during VOICE, and subsequently enrolled in an MTN ancillary study (MTN-015 for those who acquired HIV and MTN-016 for those who became pregnant), may continue to participate in these studies.

Following the promising results of CAPRISA 004, which found tenofovir gel 39 percent more effective than placebo gel when used before and after sex, the U.S. Food and Drug Administration indicated that it would review data from VOICE as the second pivotal trial to support possible licensure of tenofovir gel. However, instead of providing clear evidence of tenofovir gel’s efficacy, VOICE has provided clear evidence that the gel was not effective in the women in the study, who were asked to use the gel every day. Although disappointing, this information adds a critical dimension to discussions about the future of tenofovir gel. Of note, FACTS 001, a Phase III trial testing the same regimen of tenofovir gel used in CAPRISA 004, plans to continue its study. FACTS 001 began enrolling participants in October and will involve approximately 2,200 women at up to nine sites in South Africa, with results expected in 2014.

Investigators will not be able to determine why tenofovir gel was not effective in the women in VOICE until after the study is completed and all of the data is analyzed in full. The investigators, led by Zvavahera Mike Chirenje, M.D., of the University of Zimbabwe in Harare, and Jeanne Marrazzo, M.D., M.P.H., from the University of Washington in Seattle, U.S., expect to complete all follow-up of participants by mid-2012. Study results are expected to be available in late 2012 or early 2013.

The VOICE team acknowledges with extreme gratitude the women who have participated in the trial, who have helped in providing the answers to key scientific questions, first about oral tenofovir tablets, and now about tenofovir gel. The goal now is to complete the study so that we can determine whether Truvada used daily is safe and effective in preventing HIV in women.

VOICE is especially relevant for understanding the potential for Truvada to prevent HIV in different groups of women. While two studies – Partners PrEP and TDF2 – showed that daily use of Truvada was very effective in both the men and women in those studies, it is not certain how generalizable the data from these two studies are to all women. Partners PrEP found Truvada was 73 percent more effective than placebo among men and women in committed relationships with an HIV-infected partner, in which both partners knew each other’s HIV status and both consented to enroll in the study. As such, the results may not represent single women, women with multiple partners or those who, though married, may not know whether or not her husband has HIV. And while the results of TDF2 suggest that Truvada was effective in both men and women, few conclusions can be drawn from the results concerning the effectiveness of Truvada specifically in women due to the small numbers of women who became infected during follow-up.

The one trial besides VOICE that involved only women, a study called FEM-PrEP, was not able to demonstrate that daily use of Truvada was effective in that study population of women who were considered higher-risk, including women who engaged in frequent sexual intercourse or had more than one sex partner. A full analysis of FEM-PrEP data is expected to be available at the end of 2011 or early 2012, at which time there will be greater understanding why the study could not find Truvada effective.

A DSMB is an independent group of clinical research experts, statisticians, ethicists and often community representatives that provides additional oversight to a clinical study. A DSMB regularly reviews blinded data not available to the investigators or anyone else, while a clinical trial is in progress. Based on its review of interim data, a DSMB may, at any time, recommend that a trial, or part of a trial, be stopped if there are concerns about safety, compelling evidence for a product’s effectiveness or if it becomes clear that the trial cannot show that a product is effective, a concept called futility.

Since the study began in September 2009, the NIAID Prevention Trials DSMB has conducted six periodic reviews of VOICE interim data. All reviews prior to the September 2011 review indicated no concerns, and the DSMB

**-more-**

recommended each time that the study continue, without changes. The Nov. 17 DSMB review was the study's fourth review of safety data and the third and final interim review of efficacy data – an assessment of the number of HIV infections that have occurred in each of the different study groups since the study began.

Globally, women account for 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual intercourse is the primary driver of the epidemic. Young women are especially vulnerable. In southern Africa, young women are up to five times more likely to become infected with HIV than young men, and more than a quarter (26 percent) of all new global HIV infections occur in women aged 15-24. Women are twice as likely as their male partners to acquire HIV during sex. Although correct and consistent use of male condoms has been shown to prevent HIV, women are not always able to negotiate their use. Women desperately need methods for preventing HIV that they can control themselves. ARV-based prevention methods – as either a vaginal gel or an oral tablet – are promising approaches.

Oral tenofovir (tenofovir disoproxil fumarate), known by the brand name Viread<sup>®</sup>, and Truvada, a combination tablet that contains tenofovir and emtricitabine, are both approved for the treatment of HIV when used in combination with other ARVs. Viread and Truvada are registered trademarks of Gilead Sciences, Inc., of Foster City, Calif., U.S. Both have been evaluated in clinical trials in different at-risk populations to determine if they can prevent HIV in people who are HIV-negative. Prior to the Partners PrEP, TDF2 and FEM-PrEP studies, the iPrEx study found Truvada – together with a comprehensive HIV prevention package – was safe and 44 (43.8) percent more effective than a placebo tablet for protecting against HIV in men who have sex with men (MSM). iPrEx-OLE, an open-label extension trial of Truvada in MSM is underway at trial sites in South America, the U.S., Thailand and South Africa. Results of a trial testing the effectiveness of oral tenofovir taken daily for reducing the risk of HIV among 2,400 injection drug users in Thailand, which was conducted by the U.S. Centers for Disease Control and Prevention, are anticipated in 2012

Tenofovir gel is a vaginal microbicide that contains the same active ingredient as the oral tablet formulation of tenofovir. Microbicides are products designed to prevent or reduce the sexual transmission of HIV when applied topically on the inside of the vagina or rectum. In 2006, Gilead assigned a royalty-free license for tenofovir gel to CONRAD, of Arlington, Virginia, and the International Partnership for Microbicides of Silver Spring, Maryland. CONRAD has been leading all discussions with drug regulatory authorities and working to ensure that different requirements are met. In June 2011, CONRAD and the South African government's Technology Innovation Agency (TIA) announced a license agreement that grants TIA the rights to manufacture and distribute tenofovir gel in Africa if it is proved effective in current trials and subsequently receives regulatory approval.

MTN leadership, along with its NIH funders, are currently considering how the VOICE DSMB outcome will impact its other tenofovir gel-related trials that are either in progress or were anticipated to be starting soon. The MTN's investigation of a reformulated version of tenofovir gel for rectal use is not likely to change, with a Phase II study being planned to test the safety and acceptability of the reformulated gel used daily or before sex by men who have sex with men (MSM) at trial sites in Peru, South Africa, Thailand and the United States.

In June or July of next year, MTN researchers will be launching a Phase III trial of a vaginal ring containing the ARV dapivirine. ASPIRE – A Study to Prevent Infection with a Ring for Extended Use – will enroll approximately 3,475 women at sites in Malawi, Uganda, South Africa, Zambia and Zimbabwe. Unlike tenofovir gel, which women have had to use either daily or before and after sex, the dapivirine ring stays in place for four weeks at a time.

# # #

Additional information about VOICE, including a Questions and Answers document about the study being modified can be found at <http://www.mtnstopshiv.org/news/studies/mtn003> A summary of recent trial results of other PrEP studies can be found at <http://www.avac.org/ht/d/sp/i/326/pid/326>

#### About the MTN

*The Microbicide Trials Network (MTN) is an HIV/AIDS clinical trials network established in 2006 by the National Institute of Allergy and Infectious Diseases (NIAID), part of the U.S. National Institutes of Health (NIH). The MTN brings together international investigators and community and industry partners who are devoted to reducing the sexual transmission of HIV through the development and evaluation of products applied topically or administered orally, working within a unique infrastructure specifically designed to facilitate the research required to support licensure of these products for widespread use.*