Tenofovir Microbicide Gel Falters in Major HIV Prevention Study

November 28, 2011

HIV prevention efforts have suffered a major setback following a Microbicide Trials Network (MTN) announcement that a vaginal gel containing the antiretroviral tenofovir has been dropped from a large ongoing clinical trial because of lackluster effectiveness. The decision to discontinue the microbicide in the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study was unexpected and contradicts the optimistic results of an earlier study of the same tenofovir-based gel.

Following the promising results of CAPRISA 004, which found that women using the tenofovir gel were 39 percent less likely, overall, to become infected with HIV than women who received a placebo gel, the U.S. Food and Drug Administration (FDA) indicated that it would review data from VOICE as the second pivotal trial to support possible approval of the microbicide. However, instead of providing clear evidence of the gel's efficacy, states the MTN announcement, "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."

VOICE is being conducted at 15 trial sites in Uganda, South Africa and Zimbabwe and has enrolled 5,029 sexually active HIV-negative women. It was originally designed to compare five study groups, containing roughly 1,000 women each: the tenofovir gel, an inactive placebo gel, oral tenofovir, oral Truvada (tenofovir plus emtricitabine) and an inactive placebo tablet.

The study has already been amended once. In September, MTN said that it had discontinued the comparison of daily oral tenofovir to placebo, in light of projections that the clinical trial will not be able to demonstrate effectiveness. According to the September 28 announcement, VOICE would continue evaluating the safety and efficacy of Truvada along with the tenofovir gel. In light of the most recent announcement, released November 25, VOICE will move forward with one comparison: daily oral Truvada versus placebo.

According to the most recent review by the Data and Safety Monitoring Board (DSMB), conducted November 17, the rates of new HIV infections were nearly identical among women assigned to receive daily tenofovir gel (6 percent) or daily placebo gel (6.1 percent). Based on this lack of difference, the DSMB recommended discontinuing the tenofovir gel and placebo gel groups.

The study researchers will not be able to determine why the tenofovir gel was not effective in the women in VOICE, compared with those participating in CAPRISA 004, until after the study is completed and all of the data are analyzed in full. The investigators, led by Zvavahera Chirenje,

MD, of the University of Zimbabwe in Harare, and Jeanne Marrazzo, MD, MPH, from the University of Washington in Seattle, expect to complete all follow-up of participants by mid-2012. Study results are expected to be available in late 2012 or early 2013.

Despite two major early blows to its research objectives, MTN notes that VOICE remains 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 applicable these data are for all women.

Partners PrEP found Truvada was 73 percent more effective than placebo among men and women in committed relationships with an HIV-positive 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 their husbands have HIV.

TDF2 also suggested that Truvada was effective in both men and women. However, few conclusions can be drawn from the results concerning the effectiveness of Truvada for women, given the small numbers of women who became infected during the treatment or placebo groups 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 of why the study could not find Truvada effective.

As for the future of the tenofovir gel, at least one clinical trial is continuing as planned. The FACTS 001 study, comparing daily tenofovir gel to daily placebo gel, began enrolling participants in October and will involve about 2,200 South African women, with results expected in 2014.

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 ages 15 to 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," stresses the MTN announcement. "Antiretroviral-based prevention methods—as either a vaginal gel or an oral tablet—are promising approaches."

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