Final results of the HIV prevention study VOICE published

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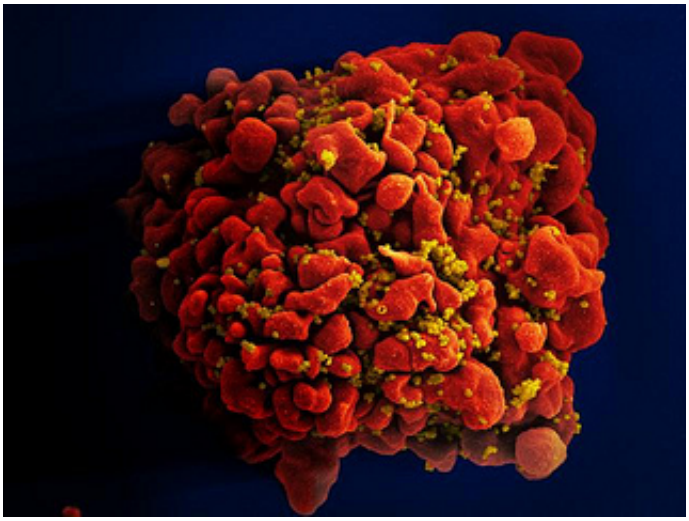

Scanning electron micrograph of an HIV-infected H9 T cell. Credit: NIAID

Researchers who conducted VOICE, a major HIV prevention trial involving more than 5,000 women in Africa, describe the study's primary results in this week's issue of the *New England Journal of Medicine* (*NEJM*), outlining in detail how the three products tested were safe but overall not effective in preventing HIV.

The study also reports the degree to which women did not use the products daily as instructed, with tests of blood indicating that just three months into the trial a majority of study participants were not using their assigned product - either an antiretroviral (ARV) tablet (tenofovir or

Truvada) or a vaginal gel (tenofovir gel). Such tests would have detected the presence of drug had there been recent use of a study product. For many women, drug was not detected in any blood sample taken at any time during the study, suggesting they may have never used the products at all.

However, among women in the tenofovir gel group whose blood tests indicated use of the gel, HIV risk appeared to be reduced significantly, additional analysis showed.

Results for the study as a whole found tenofovir gel reduced the risk of HIV by only 14.7 percent compared to a placebo gel, a finding that was not statistically significant. Estimates of effectiveness for both oral tenofovir and Truvada were less than zero (-49 percent for tenofovir and -4.4 percent for Truvada). There were no safety concerns associated with any product.

VOICE - Vaginal and Oral Interventions to Control the Epidemic— was conducted by the U.S. National Institutes of Health-funded Microbicide Trials Network (MTN) from September 2009 to August 2012. The study enrolled 5,029 women from 15 clinical research sites in Uganda, South Africa and Zimbabwe.

Most women remained in the study, keeping up with the monthly schedule of clinic visits. Moreover, adherence to daily product use was calculated to be about 90 percent based on what the participants themselves had reported to trial staff and on monthly counts of unused gel applicators and leftover pills. Tests of stored blood samples told a different story, however.

In a cohort of 647 participants randomly selected from among those assigned to use an active product, drug was detected in 29 percent of blood samples from women in the Truvada group, 30 percent of samples

in the oral tenofovir group and 25 percent among those in the tenofovir gel group.

Those least likely to use their assigned products were single women under age 25, who were also the most likely to acquire HIV. In fact, incidence in this group was nearly 10 percent at some study sites in South Africa, meaning that for every 100 women, 10 became infected per year. Overall HIV incidence in the study was 5.7 percent, nearly twice the rate the team expected before the trial.

"What we've learned from VOICE has been extremely valuable. It's been eye-opening for all of us involved in HIV prevention, particularly on trials focused on meeting the needs of women. We need to better understand women's perceived motivations for participating in a trial, but more importantly, what products they will want to use," commented Jeanne Marrazzo, M.D., M.P.H., from the University of Washington in Seattle, who led the study with Zvavahera Mike Chirenje, M.D., from the University of Zimbabwe-University of California San Francisco (UZ-UCSF) in Harare.

The study's cohort analysis revealed a persistent pattern of nonadherence that began almost from the study's start, with a woman's nonuse early in the trial largely predictive of low adherence to product use throughout.

Drug was detected in less than 40 percent of the samples of women in the cohort three months into the study, when the first samples were drawn. Most of these women had no drug detected in blood samples from later quarterly visits either, which was the case for 70 percent of women in the Truvada group, 83 percent in the tenofovir group and 72 percent in the tenofovir gel group.

Further analysis found that women in the tenofovir gel arm who had drug detected in the sample taken at their first quarterly visit were 66

percent less likely to acquire HIV than those who did not have drug detected, a result that was statistically significant. In contrast, there was no association between product use and HIV protection with either of the two tablets.

"Although the numbers are quite small, and there are other inherent limitations with this kind of analysis, we are nonetheless very encouraged to see an association between tenofovir gel use and HIV protection, especially as we await the results of the FACTS 001 study," said Dr. Chirenje, referring to the Phase III confirmatory trial of tenofovir gel used before and after sex, the results of which are expected to be reported at the upcoming Conference on Retroviruses and Opportunistic Infections (CROI).

VOICE investigators also report in the *NEJM* that as with other trials of ARV-based prevention, HIV drug resistance was very rare. Among 301 participants who acquired HIV after randomization, there was one case of emtricitabine resistance detected.

Women represent more than half of all people living with HIV worldwide and account for nearly 60 percent of those with HIV in sub-Saharan Africa. Efforts to promote abstinence, monogamy and the use of male condoms have not been enough to stop the epidemic nor are these approaches practical in many settings.

"We remain committed to finding ways that women can protect themselves against HIV and are hopeful that methods that are less dependent on adherence, such as the monthly dapivirine vaginal ring we are currently evaluating in the ASPIRE study, will help make a difference," Dr. Chirenje added.

Provided by Microbicide Trials Network