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Final results of the HIV prevention study VOICE are published in NEJM
Secondary analysis suggests many women in the trial probably never used the products
but those who did use tenofovir gel had lower risk of HIV

PITTSBURGH, Feb. 4, 2015 – 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.

In addition to Drs. Marrazzo and Chirenje, authors of the NEJM study are: Gita Ramjee, Ph.D. (South Africa); Barbra A. Richardson, Ph.D. (U.S.); Kailazarid Gomez, M.P.A. (U.S.); Nyaradzo Mgodzi, M.Med. (Zimbabwe); Gonasagrie Nair, M.B., Ch.B., M.P.H. (South Africa); Thesla Palanee, Ph.D. (South Africa); Clemensia Nakabiito, M.Med. (Uganda); Ariane van der Straten, Ph.D. (U.S.); Lisa Noguchi, M.S.N., Ph.D. (U.S.); Craig W. Hendrix, M.D. (U.S.); James Y. Dai, Ph.D. (U.S.); Shayhana Ganesh, M.Med. (South Africa); Banningi Mkhize, M.B., Ch.B. (South Africa); Marthinette Taljaard, B.S. (South Africa); Urvi M. Parikh, Ph.D. (U.S.); Jeanna Piper, M.D. (U.S.); Benoît Mâsse, Ph.D. (Canada and U.S.); Cynthia Grossman, Ph.D. (U.S.); James Rooney, M.D. (U.S.); Jill L. Schwartz, M.D. (U.S.); Heather Watts, M.D. (U.S.); Mark A. Marzinke, Ph.D. (U.S.); Sharon L. Hillier, Ph.D. (U.S.); Ian M. McGowan, M.D. (U.S.).

Some of the study's primary results were previously reported at CROI in March 2013.

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Tenofovir and Truvada are both approved for the treatment of HIV when used in combination with other ARVs. Tenofovir (tenofovir disoproxil fumarate, or TDF) is known by the brand name Viread[®]. Truvada is the brand name for a tablet containing both tenofovir and emtricitabine. In July 2012, the U.S. Food and Drug Administration approved the use of Truvada also for HIV prevention (pre-exposure prophylaxis, or PrEP) based largely on the results of two pivotal trials in two different populations – the iPrEx study in 2,500 men who have sex with men (MSM), and the Partners PrEP Study involving 4,758 serodiscordant heterosexual couples in whom one partner is HIV-infected. These and other studies have shown Truvada is more effective when used consistently. Indeed, as with VOICE, Truvada was not effective in the FEM-PrEP Study of 2,119 women in whom adherence was very low.

Tenofovir gel used before and after sex was found to reduce the risk of HIV by 39 percent in the CAPRISA 004 study, which was considered a major milestone for the field. The study, which involved 889 women at two sites in South Africa, found tenofovir gel also reduced the risk of HSV-2 by 51 percent, the first time a biomedical prevention method was shown to protect against HSV-2. A secondary analysis of VOICE data found HSV-2 risk was reduced by 46 percent in women who used the gel regularly. FACTS 001 is a Phase III trial of 2,059 women in South Africa that aims to confirm CAPRISA 004 results for both HIV and HSV-2, with results anticipated early 2015. Also under investigation by MTN researchers is a reduced glycerin formulation of tenofovir gel for use as a rectal microbicide. MTN-017 is a Phase II trial involving 186 men who have sex with men (MSM) and transgender women in Peru, South Africa, Thailand, the United States and Puerto Rico. Results are expected late 2015 or early 2016.

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 with co-funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Institute of Mental Health, all components of the U.S. National Institutes of Health. Based at Magee-Womens Research Institute and the University of Pittsburgh, the MTN brings together international investigators and community and industry partners whose work is focused on the development and rigorous evaluation of promising microbicides – products applied inside the vagina or rectum that are intended to prevent the sexual transmission of HIV – from the earliest phases of clinical study to large-scale trials that support potential licensure of these products for widespread use. More information about the MTN is available at www.mtnstopshiv.org

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