# Daily HIV prevention approaches didn't work for African women in the VOICE study

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Results of a major HIV prevention trial suggest that daily use of a product – whether a vaginal gel or an oral tablet – does not appear to be the right approach for preventing HIV in young, unmarried African women.

Of the three products tested in the VOICE Study – tenofovir gel, oral tenofovir and oral Truvada® – none proved to be effective among the 5,029 women enrolled in the trial; most participants did not use them daily as recommended. Drug was detected in less than a third of blood samples from women who were assigned to use either Truvada or oral tenofovir and in less than a quarter of samples from women designated to use gel. Moreover, those least likely to use their assigned products, single women under age 25, were also the most likely to acquire HIV. Incidence in these young women approached nearly 10 percent in some of the study sites in South Africa, a rate considerably higher than expected, according to study results presented at the 20th Conference of Retroviruses and Opportunistic Infections (CROI) in Atlanta.

"Although there may be other explanations for why these products don't always work to prevent HIV, it's hard to ignore the fact that that so few women in our study used them. Clearly, an approach of daily product use is not going to work for the population of women who participated in VOICE. Equally important, the women in our study—especially in South Africa—experienced rates of HIV acquisition that were much higher than we expected. The bottom line is that this group of young women remains at very high risk of HIV infection, and urgently needs safe,

effective and practical HIV prevention methods that they will actually use," said Jeanne Marrazzo, M.D., M.P.H., who reported the results on behalf of a team of investigators from 15 trial sites in Uganda, South Africa and Zimbabwe.

VOICE – Vaginal and Oral Interventions to Control the Epidemic – was conducted by the U.S. National Institutes of Health-funded Microbicide Trials Network (MTN) and led by Zvavahera Mike Chirenje, M.D., of the University of Zimbabwe in Harare, and Dr. Marrazzo, from the University of Washington in Seattle.

"No intervention is going to be effective if it's not used, and the point is that the majority of women in VOICE didn't use any of the study products as recommended. So, while we are disappointed in these results, we have answered the questions VOICE was designed to answer, and what we have learned is critically important," Dr. Chirenje added.

Although other studies in other populations have shown that with consistent use, both oral Truvada and oral tenofovir are highly effective for reducing the risk of HIV, the VOICE results confirm those of the FEM-PrEP study, which tested daily use of Truvada and involved a very similar population of women. As in VOICE, most FEM-PrEP participants didn't follow the daily regimen.

VOICE, which began enrolling women in September 2009, was designed to evaluate whether antiretroviral (ARV) drugs commonly used in treating HIV are safe and effective in preventing sexual transmission of HIV in women as either a vaginal gel or an oral tablet used daily, an approach called oral pre-exposure prophylaxis, or PrEP. VOICE originally had five study groups. Participants were randomly assigned to use either tenofovir gel or a placebo gel (with no active ingredient), or one of three tablets: tenofovir (known by the brand name Viread®), Truvada (the brand name for a tablet containing both tenofovir and

emtricitabine) or an oral placebo. Participants were asked to use their assigned products daily, and all received ongoing HIV risk-reduction counseling, condoms, and diagnosis and treatment of sexually transmitted infections (STIs) – standard approaches for reducing the risk of HIV – throughout the trial.

In late 2011, VOICE stopped testing oral tenofovir and tenofovir gel after separate routine reviews of study data by an independent group of experts determined that while each was safe, neither was effective in preventing HIV compared to the matched placebos among the women in those groups. Because the study was ongoing and still blinded, study investigators did not know why these products were not effective. VOICE continued to evaluate Truvada until the scheduled end of the study in August 2012.

At CROI, Dr. Marrazzo reported that 312 of the 5,029 women enrolled in VOICE acquired HIV during the study, for an overall HIV incidence of 5.7 percent, nearly twice the rate that investigators had expected when they designed the trial. (Another 22 women were later identified to be infected at enrollment and excluded from the analysis, which was based on 5,007 participants.) HIV incidence, which reflects the number of women who become newly infected for every 100 participants in a given year, ranged from 0.8 percent in Zimbabwe, to 2.1 percent in Uganda, to 7 percent in South Africa. It was nearly 10 percent at some South African trial sites.

No safety concerns were identified for any of the products, yet the study found that, like oral tenofovir and tenofovir gel, daily use of Truvada was not an effective strategy, with 61 of 994 women in the Truvada group acquiring HIV (4.7 percent HIV incidence) compared to 60 of 1,008 in the oral placebo group (4.6 percent incidence).

Of the 1,002 women in the oral tenofovir group, 60 acquired HIV. HIV

incidence, however, was calculated to reflect what had occurred up until Oct. 3, 2011, when sites began informing participants that testing of oral tenofovir was to stop. At this time, there were 52 infections in the tenofovir tablet group and 35 in the oral placebo group, for HIV incidence rates of 6.3 and 4.2 percent, respectively. Of the 1,003 women assigned to use tenofovir gel, 61 women acquired HIV (5.9 percent HIV incidence), and 70 infections occurred among the 1,000 women in the placebo gel group (6.8 percent HIV incidence). Though the estimates of effectiveness for both oral tenofovir and Truvada were less than zero, tenofovir gel was estimated to reduce the risk of HIV by 14.7 percent compared to the placebo gel, but with a confidence interval indicating the level of effectiveness could be between -21 percent and 40 percent, this finding was not statistically significant.

An analysis of blood samples from a subset of 773 participants (including 185 women who acquired HIV) found adherence to product use was low across all groups: drug was detected in 29 percent of blood samples from women in the Truvada group, 28 percent of samples in the oral tenofovir group and 23 percent among those in the tenofovir gel group. In sharp contrast, adherence to 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.

Perhaps most concerning to the researchers were the study's findings highlighting the gravity of the epidemic in a population that continues to be among the most vulnerable: young, single women. HIV incidence was 8.8 percent for unmarried women younger than 25 compared to 0.8 percent for older women who were married, differences that were statistically significant. Moreover, young, single women were much less likely to use their assigned study product. In the Truvada group, for example, drug was detected in the blood of just 21 percent of younger, single women compared to 54 percent of those married and over age 25.

The team hopes to understand why women did or did not use the products, including how perception of HIV risk may have played a role. Analysis is ongoing of two qualitative behavioral studies, VOICE C and VOICE D, with results expected in the coming months. Examination of drug levels in vaginal fluid is also planned, which should provide greater insight into the relationship between product use and product efficacy, particularly for tenofovir gel.

Other results still to be reported include a secondary analysis that is hoped will provide information about the potential of tenofovir gel to reduce the risk of herpes simplex virus (HSV-2), and results of the Bone Density Sub-study (VOICE B). VOICE B is an observational study in a subset of VOICE participants designed to explore the effects of oral study products on bone health. Participants are being followed until August 2013, and results are expected before the end of the year.

"In VOICE, our primary aim was to determine the safety and effectiveness of vaginal and oral products used daily, but also to learn which approach the women in our study would prefer. They apparently wanted neither," commented Sharon Hillier, Ph.D., of the University of Pittsburgh School of Medicine, who with Ian McGowan, M.D., Ph.D., is co-principal investigator of the MTN. "Products that are long-acting, such as the dapivirine vaginal ring, which we are evaluating in the ASPIRE study, and that women use for a month at a time, may be more suitable for this vulnerable population."

Women account for 60 percent of adults with HIV in sub-Saharan Africa, where unprotected heterosexual intercourse is primarily to blame for the region's heavy HIV burden. Young women are especially vulnerable. Efforts to promote abstinence, monogamy and male condom use haven't been enough to stop the HIV epidemic nor are these methods feasible in most settings. There is an urgent need for effective strategies that women can control themselves and be willing to use.

Of the 5,029 women enrolled in VOICE, 4,077 were from South Africa, 322 from Uganda and 630 were from Zimbabwe. The mean age was 25.3 (nearly half were younger than 25); and 79 percent of the participants were single. In South Africa, the mean age was 24.7, although more than half (55 percent) were under age 25 and only 8 percent were married. In contrast, the mean age in Uganda and Zimbabwe, was 28.3 and 28.1, respectively; 50 percent of the women enrolled in Uganda were married, while in Zimbabwe, 94 percent were married.

VOICE was funded by the National Institute of Allergy and Infectious Diseases (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 products were provided by Gilead Sciences, Inc., of Foster City, Calif., and by CONRAD, of Arlington, Va. Viread (oral tenofovir) and Truvada are registered trademarks of Gilead Sciences. In 2006, Gilead assigned a royalty-free license for tenofovir gel to CONRAD and the International Partnership for Microbicides of Silver Spring, Md.

Tenofovir and Truvada are both approved for the treatment of HIV when used in combination with other ARVs. In July 2012, the U.S. Food and Drug Administration approved the use of Truvada also for HIV prevention, a decision 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 heterosexual couples in which one of the partners has HIV. In iPrEx, there were 42 percent fewer HIV infections in the Truvada group compared to the placebo group. Partners PrEP, which tested both tenofovir and Truvada, found daily use of Truvada reduced HIV risk by 75 percent and 67 percent with tenofovir. TDF2, a smaller study in 1,200 heterosexual men and women also found Truvada effective, with a

62.6 percent reduction in HIV risk compared to placebo. These same studies also demonstrated that Truvada was more effective in protecting against HIV when the daily regimen was followed consistently. Indeed, Truvada was not effective in the FEM-PrEP Study, and many of its participants, 2,119 women from Kenya, South Africa and Tanzania, didn't take the tablets.

In July 2012, the World Health Organization (WHO) issued guidance on PrEP for serodiscordant couples (in whom one partner is HIV-infected) and MSM, recommending its use only in the context of demonstration projects. WHO expects to issue formal PrEP implementation guidelines in 2015 that will consider emerging evidence from trials such as VOICE, as well as outcomes of in-country demonstration projects. Information about Truvada and its "real world" use is being collected in open-label trials, such as iPrEx OLE and the Partners Demonstration Project, and in several other demonstration projects and implementation studies taking place in the United States.

Tenofovir gel used before and after sex was found to reduce the risk of HIV by 39 percent in the CAPRISA 004 study, a finding that was considered a major milestone for the field. The study, which involved 889 women at two sites in the KwaZulu-Natal province of South Africa, unexpectedly found that tenofovir gel also reduced the risk of HSV-2 by 51 percent, the first time that any kind of biomedical prevention method was shown to be effective against HSV-2. FACTS 001, an ongoing Phase III trial of the same regimen used in CAPRISA 004 (before and after sex) that plans to enroll 2,900 women at nine South African sites, hopes to replicate the CAPRISA 004 findings, with results expected in 2015. Concurrently, former CAPRISA 004 participants are being invited to enroll in CAPRISA 008, an open-label follow-on study looking at the feasibility of gel delivery through family planning services.

In other MTN studies, researchers are evaluating a reduced glycerin

formulation of tenofovir gel. In one trial to be conducted in South Africa and the United States, researchers will examine drug absorption patterns in both rectal and vaginal tissue when the gel is applied either vaginally or rectally, while a Phase II trial, MTN-017, hopes to determine whether the reformulated gel is safe and acceptable as a rectal microbicide among men who have sex with men (MSM) and transgender women in Peru, South Africa, Thailand and the United States. MTN-017, which is the first Phase II trial of a rectal microbicide, is expected to begin mid-2013.

Provided by Microbicide Trials Network