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Behavioral Measures of Product Use Didn't Measure Up in VOICE HIV Prevention Trial, Report the Study's Researchers

BOSTON, March 4, 2014 – A new analysis by researchers from the U.S. National Institutes of Health-funded Microbicide Trials Network (MTN) confirms what they and many others had already assumed: The behavioral measures used for assessing adherence in the VOICE study – an HIV prevention trial that involved more than 5,000 women in sub-Saharan Africa – did not provide accurate information about women's use and nonuse of the products being tested. Their results, which were reported at the 21st Conference on Retroviruses and Opportunistic Infections (CROI) in Boston today, found these tools were not much better than chance at being able to predict adherence to product use.

"In settings where VOICE was conducted, asking a participant whether or not she is taking her tablets or using her gel provided little insight into her actual behavior. Of course, it's critical to understand the reasons why women chose to say one thing and do another, and in that regard, conducting interviews and other socio-behavioral assessments will remain extremely important," said Ariane van der Straten, Ph.D., M.P.H., of the RTI International/Women's Global Health Imperative (RTI/WGHI) program in San Francisco, the lead behavioral scientist for the VOICE study team.

"However, for assessing adherence to product use in the context of an HIV prevention trial, our data is very persuasive that biological measures can provide a more accurate picture," she added.

VOICE – Vaginal and Oral Interventions to Control the Epidemic – evaluated different antiretroviral (ARV)-based approaches for preventing HIV among 5,029 women from 15 sites in South Africa, Uganda and Zimbabwe between 2009 and 2012. The study's primary results, which were presented at last year's CROI meeting, found none of the products tested (tenofovir tablets, Truvada® tablets and tenofovir vaginal gel) was effective in preventing HIV among the study's participants, who were asked to use their assigned product daily. Although the behavioral measures of adherence indicated that 90 percent of the women had followed the daily regimens, tests of stored blood samples conducted at the end of the trial revealed that only 25 percent had actually used product regularly.

With such disparate findings, the researchers decided to evaluate the predictive value of the methods they had used to measure adherence. These included a questionnaire that was administered by staff at every monthly visit asking about product use within the last seven days; and at quarterly visits, use of a computer-based system called Audio Computer-Assisted Self Interview (ACASI) that asked many of the same questions. Because the greater privacy afforded to participants, it was envisioned ACASI would allow for more honest responses about product use than perhaps women would be be willing to give in face-to-face interviews. Records were also kept of the number of leftover pills and unused applicators participants returned each month. Objective measurements involved analysis of stored biological samples at the end of the study to detect the presence of drug – a clear indication whether or not product had been used. All participants had blood samples drawn at their quarterly study visits, and participants assigned to use gel also had vaginal fluid samples taken every six months.

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For their analysis, the researchers examined data from a cohort of 472 women who had been assigned to use an active product and had available from at least one follow-up visit both their responses to ACASI questions and drug level results. The cohort comprised 312 women who had been assigned to take an oral tablet (157 in each the tenofovir tablet and Truvada tablet groups) and 158 women who had been assigned to use tenofovir gel.

Based on the ACASI data, 91 percent of the women in the oral tablet groups and 90 percent of the women in the vaginal gel group reported using their assigned product at least once in the week prior to the study visit. In these same women, however, blood tests indicate that 31 percent of women had used the tablets at least once within the past week and, similarly, tests of vaginal fluid show 36 percent of the women had recently used the gel.

The analysis did not seek to explain why so many women had not used the study products or why so few women were able or willing to admit nonuse. However, two social and behavioral research sub-studies of VOICE – VOICE C and VOICE D – were designed to address these and similar questions. Although VOICE D is ongoing and not expected to report results until later this year, the first set of results coming out of VOICE C were recently published in the online journal PLOS ONE.

VOICE C, also known as MTN-003C or the Community and Adherence Sub-study, was conducted in parallel with VOICE and designed to identify the specific factors and beliefs within women's communities, social groups and households that may have influenced their willingness or ability to follow the daily regimens in VOICE. It was conducted at a single site – Wits Reproductive Health and HIV Institute (Wits RHI) in Johannesburg, South Africa – and included 102 women enrolled in VOICE, as well as 26 male partners, 17 members of WRHI's Community Advisory Board (CAB) and 23 key community stakeholders, for a total of 164 participants. The results reported in PLOS ONE involve only the group of VOICE participants, who took part in a focus group discussion, a one-time in-depth interview or in a series of ethnographic interviews involving more open-ended conversation over several hours.

While most women claimed they were able to use their assigned products, they alleged other participants were not. All but two women mentioned knowing or hearing about other participants who were not following the study's regimens, often times while sitting in the clinic's waiting room. The lead authors, Dr. van der Straten and Jonathan Stadler, Ph.D., of Wits RHI, who together also led the study, suggest the reasons for women not using the study products included; worries about both the side-effects and the stigma associated with the use of products meant for people infected with HIV; ambivalence about participating in a blinded clinical trial in which it wasn't known whether they had been assigned to use an active product or a placebo, or that the active products were even effective; and pressure from loved ones or strains on relationships with partners, family and friends.

Unlike VOICE C, VOICE D was designed to be conducted after women completed their participation in VOICE, and it includes women from all three countries where VOICE was conducted. Of note, stage two of the study, which is still underway, involves individual interviews and/or focus group discussions with women assigned to use an active product during VOICE for whom stored blood samples have been tested for presence of drug. Researchers hope that when women are told whether or not drug was detected in their blood they will be more forthcoming about why they hadn't (or hadn't always) used their assigned product, or, for a minority of women, how they managed to use product consistently.

In response to VOICE, the MTN has looked to ways to both enhance and monitor product adherence in its ongoing trials so that challenges with use can be addressed as they occur. In ASPIRE, a Phase III trial of the dapivirine vaginal ring, this is being done in a way that preserves the blinded, placebo-controlled nature of the study. The unique design of MTN-017, a Phase II trial of a reduced glycerin formulation of tenofovir gel used as a rectal microbicide in men who have sex with men and transgender women, allows for routine tests of blood and the results to be shared with participants as part of their ongoing adherence counseling sessions on product use.

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.

In addition to Dr. van der Straten, other authors of the study presented at CROI are Elizabeth Brown, Sc.D. (Fred Hutchinson Cancer Research Center); Jeanne Marrazzo, M.D., M.P.H. (University of Washington); Zvavahera Mike Chirenje, M.D. (University of Zimbabwe); Kailazarid Gomez, M.P.M. (FHI 360); Jeanna Piper, M.D. (Division of AIDS, National Institute of Allergy and Infectious Diseases); and Craig Hendrix, M.D. (Johns Hopkins University).

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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.

More information about VOICE can be found at http://www.mtnstopshiv.org/news/studies/mtn003 .

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