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The VOICE C and VOICE D Social and Behavioral Research Sub-studies:
Looking for Answers about Adherence and the Women in VOICE

Making Sense of the Results of VOICE

VOICE –Vaginal and Oral Interventions to Control the Epidemic – was a major HIV prevention trial that tested the safety and effectiveness of two different approaches for preventing the sexual transmission of HIV in women: daily use of an antiretroviral (ARV) tablet (tenofovir or Truvada®) or daily use of a vaginal gel (tenofovir gel). VOICE (also called MTN-003) involved 5,029 women in Uganda, South Africa and Zimbabwe largely representative of the epidemic in sub-Saharan Africa; about half were under age 25, and most were not married.

- **VOICE results suggest that daily use of a product – whether a vaginal gel or an oral tablet – was not the right HIV prevention approach for the women in the study. None of the products was effective, and most participants had not used their assigned study products daily as recommended**.
  - Although adherence was estimated to be about 90 percent based on what participants themselves had reported during the VOICE study, and based on counts of unused applicators and leftover pills, blood tests revealed that only about 25 percent of the women had actually used product regularly. Younger, unmarried women were least likely to use study product and the most likely to acquire HIV.
  - A more detailed analysis of VOICE data, when available, will help in better understanding these results (first reported at the Conference on Retroviruses and Opportunistic Infections in March 2013) as well as answer other questions VOICE was designed to address.
- **Two social and behavioral sub-studies – VOICE C and VOICE D – hope to address some of the most baffling questions about VOICE. Topping the list: Why didn't these high-risk women use the study products?**
  - VOICE C, also known as MTN-003C or the Community and Adherence Sub-study, was conducted during VOICE and looked at the factors and beliefs within women's communities, social groups and households that may have influenced their ability and willingness to follow the daily regimens. Its first set of results was published in February 2014.
  - VOICE D, or MTN-003D, was launched after VOICE and is ongoing. It aims to better understand why women joined VOICE, and why most (91 percent) stayed in the trial, yet so few used the study products (and were willing to admit non-use), despite living in communities impacted by HIV. Interviews with participants in VOICE D are conducted by a research staff that was not involved in VOICE. The study is designed to allow for more open discussion, especially among women who had reported using their assigned product but whose blood tests indicate otherwise. Results are expected by the end of 2014.

Why are VOICE C and VOICE D important?

Absent a "gold standard" for measuring adherence, researchers have relied on multiple methods in hopes of being able to piece together as accurate a picture as possible about participants' study product use during a trial. But, what does it mean when one measure suggests high adherence but another shows just the opposite, as in VOICE? Taken alone or in combination, current measures of adherence are not telling the full story.

As such, VOICE C and VOICE D are especially important for helping to make sense of the disparate findings in VOICE, by providing greater insight about the women's attitudes and behaviors and their reasons for using or not using the products. Moreover, both studies will help in understanding women's social contexts, perceptions about HIV risk and motives for taking part in VOICE, and the deterrents to both product use and being open about these difficulties with study staff.

*What is learned in VOICE C and VOICE D may also suggest ways that HIV prevention trials can glean more accurate and meaningful information about product adherence, as well as help inform the development of products that women may find more practical and easier to use, and importantly, that they will **actually** use.*

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As with VOICE, both VOICE C and VOICE D are studies of the Microbicide Trials Network (MTN) and funded by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Mental Health (NIMH), both of the U.S. National Institutes of Health (NIH).

VOICE C at a Glance

- VOICE C was conducted in parallel with VOICE at the Wits Reproductive Health and HIV Institute (Wits RHI) in Johannesburg, South Africa, one of 15 clinical research sites for VOICE. VOICE C was designed to identify specific factors within participants' households, physical and social environs and the broader community that may have influenced their willingness or ability to follow the daily regimens in VOICE. It 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 women in VOICE C took part in either a focus group discussion at the end of their participation in VOICE, a one-time in-depth interview while still participating in the trial or in a series of ethnographic interviews, which involved a researcher spending several hours at their homes, much of this time engaging in open-ended conversation. Male partners, CAB members and community stakeholders were asked to participate in either in-depth interviews or focus groups, allowing researchers to gain insight into the community's overall acceptance and understanding of the trial, social norms around HIV prevention and rumors about the study.

- The first set of results, published 21 February, 2014 in the online journal PLOS ONE, involved only the cohort of VOICE participants. 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 researchers suggest the reasons for women not using the study products included 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; worries about both the side-effects and the stigma associated with the use of products meant for people infected with HIV; and pressure from loved ones or strains on relationships with partners, family and friends.

- The research team, led by Jonathan Stadler, Ph.D., of WITS RHI, and Ariane van der Straten, Ph.D., M.P.H., of RTI International/Women's Global Health Imperative (WGHI) program in San Francisco, are currently analyzing the data collected in VOICE C and anticipate reporting results by early 2014.

VOICE D at a Glance

- VOICE D is an ongoing sub-study that aims to better understand women's actual and reported use of study products and sexual behavior during the time they took part in the VOICE trial. Specifically, it aims to better understand why women remained in VOICE yet so few adhered to product use, despite living in communities with very high HIV incidence. It complements and expands upon VOICE C by focusing more on women's individual experiences, behaviors, beliefs and attitudes about HIV risk and ARV-based prevention, and in understanding the dynamic between trial participants and trial staff – all of which may have influenced whether or not products were used.

- 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. While it also employs in-depth interviews and focus groups discussions, an important difference is that in VOICE D these are conducted in a "neutral" location (away from the trial site) by researchers who had never interacted with participants during VOICE. These and other measures to "distance" VOICE D from the parent VOICE trial are meant to encourage honesty and candid discussions about VOICE among its former participants, who, during VOICE, may have been inclined to say what they expected the researchers wanted to hear.

- VOICE D is being conducted in two phases.

    - Phase 1, which has been completed, involved 88 women who took part in individual one-time in-depth interviews after exiting VOICE, and for 73 of these women, before the trial's results were publicly reported and shared with participants and communities. Phase 1 was designed in part to better understand women's perceptions and understanding of various risk behaviors, including anal sex. At enrollment, 17 percent of the women reported having had anal sex, and although questions about these behaviors were asked during VOICE, women may have misinterpreted their meaning or been afraid to respond honestly. Because unprotected anal sex is a major risk factor for HIV, it will be important to understand whether it was under-reported or over-reported in VOICE, especially in the context of a trial that found none of the products tested – including a vaginal gel – was effective against HIV.

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- Researchers added Phase 2 in response to VOICE results finding none of the three products (oral Truvada, oral tenofovir and vaginal tenofovir gel) was effective and that most women hadn't used them. Phase 2 is enrolling former VOICE participants who had been assigned to use an active product during the trial and whose laboratory tests of stored blood – to detect the presence of active drug – indicate what their actual product use was. The goal is to enroll between 108 and 144 women, and to include HIV-negative "high adherers" (women who had drug present in most of their blood samples), HIV-negative "low adherers" (women who never or rarely had detectable drug in their blood samples), as well as women who acquired HIV during VOICE.
- The hope is that when women learn the results of their blood tests they will be more forthcoming in the individual interview and/or focus group discussion and explain 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. For instance, did women feel compelled to use the gel or take tablets just before a study visit to please investigators, only to revert to nonuse afterward? When women enrolled in the trial, did they ever intend to use their assigned study product, or did they participate for other reasons, including for the health care services or HIV testing the study provided? If they had intended to use their assigned products, what prevented them from doing so?

- VOICE D is being led by Dr. van Straten, of RTI/WGHI, with Barbara Mensch, Ph.D., of the Population Council and Elizabeth Montgomery, Ph.D., also of RTI/WGHI.

Fast Facts about Adherence in VOICE

Participants were counseled at each visit about the importance of adhering to the study regimens, product use and safe sex practices. Moreover, participants were informed of results of other studies that found the same products effective when used consistently, such as CAPRISA 004, which tested tenofovir gel used before and after sex, and the Partners PrEP Study, which evaluated daily use of Truvada and tenofovir tablets.

Several methods were used to measure adherence in VOICE. At different time points during the trial, study staff asked participants about their sexual activity, product use, male condom use and product sharing. Similar questions were asked privately through a computer program. In addition, a record was kept of the number of leftover pills and unused applicators for each participant at every monthly visit. After the study was completed, information collected through these measures was then collated with data from objective laboratory tests to detect the presence of drug in samples of participants' stored blood, vaginal fluid and hair.

At the end of the study, an analysis of blood samples from a subset of 773 participants who had received the active products (including 185 women who acquired HIV) found adherence to product use was low across all groups. Drug was detected in less than a third of blood samples from women who were assigned to use either Truvada or oral tenofovir tablets and in less than a quarter of samples from women asked to use tenofovir gel. In sharp contrast, adherence was estimated to be about 90 percent based on self-report measures and monthly counts of unused gel applicators and leftover pills.

Younger, single women in VOICE were much less likely to use the study products than those who were older or married, and were also more likely to get infected. In the Truvada group, for example, drug was detected in the blood of just 21 percent of younger, single women compared to 54 percent for those older and married. HIV incidence, which reflects the number of women who become newly infected for every 100 participants in a given year, was 8.8 among young, unmarried women, more than 10 times higher than the HIV incidence of 0.8 for the older, married women in VOICE.

Researchers are analyzing *every* sample collected from all participants in VOICE – more than 160,000 plasma samples alone – to better understand the relationship between product use and product efficacy. The results of these analyses, which should be available sometime in 2014, are not likely to change the study's main conclusions, however.

What is adherence?

Adherence – a person's correct and consistent use of a prescribed regimen – is especially important in the context of HIV prevention clinical trials.

For instance, when adherence is high, meaning most participants use the study product as directed, researchers can determine with greater certainty whether the product prevents HIV.

But no matter how effective a given product or approach may be, it can have no benefit if it's not used; women who need safe and effective HIV prevention methods must also be willing and able to use them. As such, a finding of low adherence in a clinical trial may provide important clues about what might happen in the "real world."

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Beyond VOICE: What Other Trials Have to Say

Partners PrEP and FEM-PrEP: The Highs and Lows of Adherence

Other studies in other populations of people have shown that with consistent use ARV-based products are highly effective for preventing HIV. Indeed, this was the basis for U.S. Food and Drug Administration approval of Truvada as HIV prevention, with the results of the Partners PrEP Study providing especially convincing evidence among heterosexual couples in whom one of the partners has HIV. Adherence to product use was very high in Partners PrEP, and both tenofovir and Truvada were very effective. Importantly, these were men and women who were on average older than the women in VOICE, and all were in committed relationships with a partner they knew was infected. They may have been more motivated to use the products consistently, knowing very well they risked getting infected. Yet, like VOICE, the FEM-PrEP study did not find Truvada effective among its population of young, predominately single women, most of whom had not followed the daily pill-taking regimen as instructed.

FEM-PrEP researchers are exploring the possible reasons why women had not used their study products, including whether participants hadn't seen themselves at risk of HIV. Indeed, based on interviews with a small sample of participants at enrollment and quarterly throughout the time they were in the trial, the researchers found that 63 percent of the women perceived themselves at low or no immediate risk of HIV, yet, 28 percent had multiple partners and 74 percent reported having sex without a condom in the prior four weeks. The ongoing HIV testing and counseling and healthcare services that were provided as part of the study were important reasons the women enrolled and remained in the trial, and the researchers surmise that the reassurance of having a negative HIV test each month may have given these women an "out" for not using the product.

Aspiring to get it right: Measuring adherence in current and future HIV prevention trials

Researchers are evaluating different strategies and new prevention approaches they hope women will want and be able to use. FACTS 001 is testing tenofovir gel used before and after sex and plans to enroll 2,900 women at nine South African sites, with results expected in 2015. As sister studies, ASPIRE, which is being conducted by the MTN, and The Ring Study, which is a trial of the International Partnership for Microbicides, are both assessing whether a vaginal ring containing the ARV drug dapivirine is safe and effective for protecting against HIV when used by women for a month at a time. Results of these two studies are expected late 2014 or early 2015.

Still, the results of VOICE have caused these and other trials to reevaluate and/or strengthen their efforts to enhance product adherence, including helping current and prospective trial participants and local communities better understand the importance of product use and the impact that non-adherence can have on the findings of a research study. Many of these trials have already incorporated ways to measure and use adherence information closer to "real time," as the trial is underway. In ASPIRE, for example, participant blood samples are being tested on a routine basis to determine the presence of active drug, but in a way that preserves the blinded, placebo-controlled nature of the study. So, while the study investigators and participants don't know individual participant results, data pooled according to sites or the study overall can indicate a need to modify ongoing adherence counseling, enrollment activities or community messages about ASPIRE.

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About VOICE

VOICE, also known as MTN-003, is a flagship study of the Microbicide Trials Network. The study began September 2009 and completed follow-up of all participants in August 2012. VOICE was led by Zvavahera Mike Chirenje, M.D., from the University of Zimbabwe in Harare; and Jeanne Marrazzo, M.D., M.P.H., from the University of Washington in Seattle. 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. More information about VOICE and related sub-studies can be found at http: //www.mtnstopshiv.org/news/studies/mtn003

About the Microbicide Trials Network

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.

21-February-2014