*On Monday, March 11, AVAC hosted a global advocates' webinar to discuss the recent results from the VOICE trial and implications for ongoing and future HIV prevention research. VOICE co-principal investigator Jeanne Marrazzo presented an overview of the study findings (download her slides here) and AVAC Executive Director Mitchell Warren moderated the discussion. Below you will find a write-up of the Q&A portion of the call. The webinar recording is available for playback here.*

*Additional background, including a more extensive Q&A document from the MTN, is available at www.avac.org/voice.*

**VOICE Webinar Q&A**

***Question:*** *Were the [VOICE trial] participants aware of the issues with product adherence when they started the trial?*

**Jeanne Marrazzo:** We knew adherence was an issue, it was an issue in every study, including iPrEx [a study in MSM and transgender women that was the first PrEP study to show effectiveness]. There were three ways we monitored adherence:

1) Participants were asked to bring back unused products and empty pill bottles, including any pills they didn't take, and unused applicators full of gel. When we looked at these measures, the participant adherence was 85-90 percent – a very different level of adherence than what was found when participant drug levels were assessed.
2) Participants met in person with adherence counselors in order to try to identify barriers to adherence. Midway through the study, site staff underwent a training to help them to identify barriers to adherence, and help participants address them.
3) Audio computer self-assisted interview (ACASI) asks women to listen to an interview on a computer and estimate how many doses they took.

These are the three measures the data and safety monitor board (DSMB) saw throughout the study. We had no reason to question adherence and didn't measure the drug level until the end of study. When discussing the results with participants some asked why we didn't measure the drug to monitor and improve adherence. The VOICE results are really going to transform the field of adherence monitoring.

***Question:*** *How does the level of payment required for trial participants by the Medicines Control Council (MCC) in South Africa compare to payment in Uganda and Zimbabwe?*
**JM:** In Uganda and Zimbabwe there is no such requirement – the participants are not compensated with money. The compensation at all sites went beyond cash, including pap smears, contraception, HIV screening and other care. The package was quite generous and compelling; when we talk to participants we have to look carefully at what it was that they liked about the study and why they continued to come back for the product? Was it for the cash in South Africa? Or, was it because there was a community organized and dedicated to the participants' well-being? Everyone needs care. For the women in VOICE the HIV pill/gel did not fit into their care framework. Maybe the takeaway is that we can't plan to intervene by providing single-pathogen interventions—meaning, those that focus on a single infection.

***Question:*** *How much work is done prior to enrolling women in the study about adherence and broader health literacy?*
**JM:** We had one of the most engaged community working groups, with special retreats to help them understand and translate to the participants concepts such as efficacy, risk estimate, control groups, etc. We had at least three retreats with the CWG, not just for their own empowerment, but to help them talk to potential participants. Trial literacy and research literacy is really critical to get participants invested.

We need to think about research before trials like VOICE to assess women's readiness to use a vaginal microbicide. Do we need to think about formative research that precedes these studies where we give them a product, or a surrogate product, to see if/how they use? VOICE will change the paradigm for how we think about recruiting women.

***Question:*** *Side-effects – what do we know about what those were and what role they may have played in women's willingness to use the products?*
**JM:** We monitored side effects throughout the study and had a participant safety panel. Nothing concerning above what was expected occurred and there was no indication that there were early symptoms that prompted the women to stop using the products. Many women went on contraceptives at the time of the study, and women who were on an oral contraceptive and an oral ARV could be a concern. However, there is no indication yet that it was a player in women's decision to stop using the products.

***Question:*** *How often were women seen at the clinic and how often did they receive HIV tests?*
**JM:** Every month. We don't want them to remain on a single HIV drug if they are infected.

***Question:*** *Isn't it counter-intuitive that use of a product once a day would be more difficult than use before and after sex?*
**JM:** Daily use has two main advantages: 1) Applying vaginal product daily allows for product to build up in tissues, thus, women would have a reservoir of active product and a substantial level of protection; and, 2) not all sex is planned. You just don't know in many cases, particularly when women don't have control. However, not all women are the same – women are going to have different needs depending on how their sexual lives unfold.

***Question:*** *Can you describe any variations in age and marital status and the potential influence on adherence?*
**JM:** Slightly over half of all participants were under 25 and the rest were over 25. Most women in Zimbabwe were married; most South African women were unmarried. It turned out that those who were married, over 25 and whose primary sex partner was over 28 had more consistent product use when we looked at drug measures in the blood. These women may have had more stable lives. Older women in this trial are similar to the Partners PrEP [a study that enrolled serodiscordant couples in Kenya and Uganda and found PrEP reduces risk of HIV infection] trial participants, which enrolled both partners of a couple and showed a 70-80 percent reduction in HIV risk and good adherence. We need to know what about the Partners study design and how it was conducted enabled women to adhere and show excellent reduction in risk, and we need to determine how can we translate this to a young, vulnerable group of women.

***Question:*** *Did the VOICE study engage male partners at all?*
**JM:** Partner involvement is critical. We specifically and systematically asked participants about the social harms of the trial, i.e., if they experienced any harm or pressure as a result of participating in the study. One thing that came across is that partners have a huge impact. We could not approach partners directly, but we did have several meetings that included male partners with Community Working Groups. In VOICE C [Community and Adherence Sub-study], we enrolled men who happened to have partners in the study.

***Question:*** *What were trial participants' reactions to the results?*
**JM:** There is profound disappointment on the part of participants. They have expressed angst and many are upset that adherence turned out to be a major issue. Some participants have asked why we didn't measure the drug as time went on. The reactions differ by demographics and site and we will learn more about this in the coming weeks as our on-site teams debrief us.

***Question:*** *Will there be additional follow-up with participants?*
**JM:** Yes, behavioral scientists are working now on follow-up. We would like to go back to some participants with the knowledge of what their adherence level was and talk to them about why they did not adhere. Rhonda White of FHI 360 is leading the Community Working Group and the results dissemination in the trial communities.

***Question:*** *Can you discuss pregnancy in the trial and if/how women changed contraception choice?*
**JM:** There was a 7.8 percent pregnancy rate in the trial, which is a very good rate for this type of study [HIV prevention trials enroll women who do not intend to get pregnant and use contraception—a low pregnancy rate is a good thing.] We did look at time off product when women were pregnant, which was the main reason for product hold that we imposed. This is not likely a reason for low adherence though. We are going to take a closer look at pregnancy within subgroups, but haven't had a chance to dive in yet. We also haven't looked in detail at contraceptive switching. Lisa Noguchi [of the MTN] is looking at contraceptive patterns and HIV incidence by type of contraception.

***Question:*** *As you're asking the women why they are not adherent [to the options studied in VOICE] are you asking them if they might be more adherent to another form – ring, injectable etc.?*
**JM:** Methods that get around daily participant activity may address the issue of adherence fatigue. We need to continue to question and take a step back and look at what really is the barrier here – is it women not wanting to use something daily or not thinking they need something period? We are excited and encouraged by newer products that offer sustained drug release, like vaginal rings and possibly injectibles, but we still need to understand at a formative level what women will want and use. We can't keep thinking these solutions will be the so-called holy grail. The other thing to consider is safety with long-acting products since the products are in for a lot longer.

***Question:*** *The FACTS 001 study is looking at tenofovir gel before and after sex, and is now enrolling. How should the VOICE results be communicated, particularly in South Africa, in light of the product being tested in FACTS? What is next? For whom might daily PrEP work and what is the next set of steps in terms of demonstration projects?*
**JM:** We need to look at it separately for oral products vs. the gel. Next step for gel is dependent on the FACTS study. For the oral products it is equally complex even though there is biological evidence for tenofovir and Truvada showing that if you are fully adherent you experience significant protection [evidence from Partners PrEP and TDF2]. Yet, women in the VOICE trial basically told us that they weren't ready to use PrEP even when they are at risk. In my opinion, demonstration projects should still include oral PrEP for two reasons, 1) Women willing to enroll in demo projects may be different than those that enroll in clinical trials and, 2) We can't withhold this intervention as part of a combination prevention package when we know it works.

***Question:*** *We've struggled for years trying to talk about efficacy and effectiveness. Thinking about the future, is there a way one can imagine disentangling those two and doing a study for actual efficacy?*
JM: One way to study efficacy is to actually be sure product is present when it's supposed to be. We would need to put people on the product and measure drug levels regularly to ensure they are as adherent as they need to be to see if the product works. We would also need to not continue the people in the study who did not adhere. Clearly people who stay in the study and take drugs are not like the real world – this is where effectiveness comes in.

***Question:*** *Is there group counseling with the participants?*
**JM:** The women enrolled discuss participation on an ongoing basis. We had collective participant information sessions. This happens at the site level and is site-specific.

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More info at www.avac.org/voice; www.prepwatch.org. Additional questions can be sent to avac@avac.org.