Failed VOICE PrEP Trial Failed to Preempt Lies About Adherence

February 5, 2015

The failure of the VOICE trial of oral and vaginal gel pre-exposure prophylaxis (PrEP) was the result of low adherence among the sub-Saharan African women participants, The New York Times reports. A significant proportion of the participants apparently went to considerable lengths to lie to study investigators about their adherence to PrEP, possibly motivated to stay in the study to receive the financial incentives or other medical care related to the trial. But the study was not well structured to anticipate or cope with low actual, as opposed to self-reported, adherence.

VOICE was a randomized, placebo-controlled study of 5,029 sub-Saharan women between the ages of 18 and 45, 91 percent of whom were retained in the study, through 5,509 person-years of follow up. The women were divided into five equal groups to receive oral Truvada (tenofovir/emtricitabine) as PrEP, oral Viread (tenofovir), an oral placebo, a vaginal 1 percent Viread gel as PrEP, or a placebo gel. The participants were advised to use the products daily.

The findings of the study were published in the New England Journal of Medicine (NEJM).

The women were all tested for HIV monthly and had their blood levels of tenofovir tested every three months. Researchers measured their adherence to the respective PrEP regimens through a monthly interview and counts of returned pills, empty pill bottles or unused vaginal applicators. Additionally, every three months, adherence levels were tested by a computer-assisted self-interview.

The study was supposed to follow women for a minimum of 12 months and a maximum of three years, but portions of the study were terminated, in two stages, when it was discovered that the groups assigned to receive PrEP were not benefitting from the intervention. The data and safety monitoring board of the study recommended the cancellation of the oral Viread portion in September 2011, and the gel portion in November of that year. However the Truvada group continued through the end of the follow-up period, in August 2012.

A total of 312 women contracted HIV during the study, an incidence of 5.7 per 100 person-years. When compared with the placebos, none of the three forms of PrEP lowered the risk of HIV to a statistically significant extent in this study.

If a risk reduction figure is statistically significant, this means that the risk reduction was unlikely

the result of chance. In fact, two of the three forms of PrEP were linked to a higher risk of HIV. However, this was also not statistically significant; all that can be concluded from the trial is that PrEP essentially had no effect. When compared with the respective placebo groups, those in the Viread group had a 49 percent greater chance of contracting HIV and those in the Truvada group had a 4 percent greater chance of infection; those in the vaginal gel group had a 14.5 percent reduced risk of contracting the virus.

Participants whose blood tests indicated use of tenofovir, and therefore adherence to PrEP, were more likely to be married, older than 25 and have had more than one child. However, all of these characteristics are also associated with lower risk of HIV, meaning that the higher-risk participants were less likely to be adherent to PrEP.

There was an increase in serum creatinine levels—an indication of kidney toxicity—of 1.3 percent among those assigned to take Truvada, compared with a 0.2 percent increase among those given the oral placebo.

Among the 301 women who contracted HIV after entering the study, one person developed what is known as the M184V mutation, which indicates resistance to the emtricitabine component of Truvada. Recent research has suggested that in the rare cases when people do develop drug resistance after contracting HIV while taking Truvada as PrEP, they are much more likely to develop resistance to emtricitabine than tenofovir. This is encouraging because of the outsize importance of tenofovir among treatments for HIV.

None of the findings about PrEP's failure to lower HIV rates suggest that oral or vaginal PrEP are incapable of preventing HIV among women. The study was unable to draw any conclusions about PrEP effectiveness because adherence was so poor. Evidence suggests that many women were lying about their rates of use.

In a random sampling of blood tests to detect tenofovir, 30 percent of the samples from the oral Viread group had detectable drug, as well as 29 percent of the samples from the Truvada group and 25 percent of the samples from the vaginal gel group. In the respective three groups of participants, the blood tests of 58 percent, 50 percent, and 57 percent of the participants never detected any tenofovir use, indicating that these women may never have taken PrEP at all. (Although it is certainly possible that any number of them did take PrEP at some point, but never soon enough before giving a quarterly blood sample to yield detectable drug on the test.)

Nevertheless, women claimed to be adhering at high rates. In the respective in-person interviews and computer questionnaires about adherence, 90 percent and 88 percent of women said they had never missed a dose of PrEP. Returned pill bottles, vaginal applicators and unused pills suggested that 86 percent of the medication had been taken.

To read the New York Times story, click here.

To read the study, click here.

To read an accompanying NEJM editorial, click here.

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