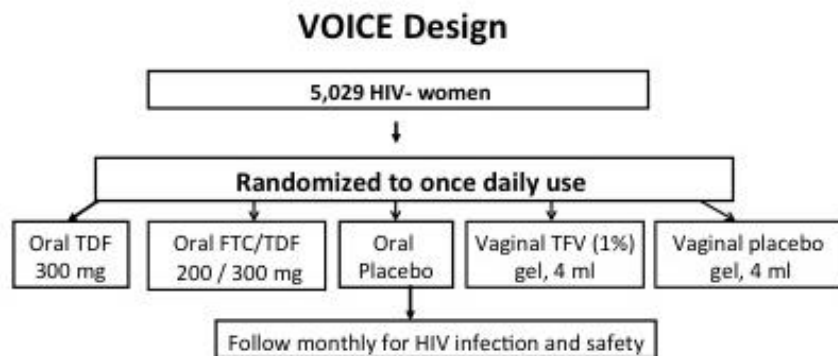# How to account for adherence in clinical trials

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Graphic showing the design of the VOICE study.

Figure provided by Dr. James Dai.

The efficacy of pre-exposure prophylaxis, a preventative strategy based on the use of antiretroviral drugs to block HIV acquisition, has been demonstrated in four different clinical trials: CAPRISA004, iPrEx, TDF2, and Partners PrEP. These studies, although different in design and target populations, showed that the utilization of such a preventive strategy is highly protective. In contrast, VOICE (Vaginal and Oral Interventions to Control the Epidemic) and Fem-PrEP studies led to the opposite conclusion. These conflicting results are likely due to low adherence to the study drug. In VOICE, for example, the plasma concentration of tenofovir, the protective drug, was detectable in less than 40% of the enrolled women.

To evaluate the real' effect of the drug, it is imperative to use an analytical method that takes participant adherence to the study protocol into account. But this is not the whole story. In fact, while we can discriminate between adherers and non-adherers in the drug study arm, we cannot easily differentiate between these groups in the placebo arm. Comparing adherers in the drug arm to non-adherers in the drug arm can be confounding. What if the subjects that adhered to the drug are also those less exposed to HIV? In such a situation, we would be comparing apples and oranges. This is likely the case for the two dissenting studies. In the same VOICE study, in fact, women that were less likely to adhere to the drug were younger and unmarried, with a higher risk score for HIV acquisition. Furthermore, while conventional statistical wisdom is to remove confounding by adjusting for confounding variables in regression models, unmeasured confounding is always possible.

Dr. James Dai at the Vaccine and Infectious Disease Division at Fred Hutch undertook this challenge and published a statistical method that allows investigators to assess whether their covariate adjustments are adequate to remove confounding errors. The method is built upon a reasonable assumption, known as " exclusion restriction" in the causal inference literature, that those with no pharmacological evidence of adherence should not receive protection from ARV. The paper was published last month on the Journal of Infectious Diseases.

Dr. Dai applied his method to the results obtained from the VOICE study, which was designed to evaluate the efficacies of a gel formulation and two oral regimens of tenofovir (TDF), alone or in combination with emtricitabine (FTC/TDF). For the comparison between tenofovir gel and placebo, adjusting for a set of confounding variables related to HIV exposure largely removed the selection bias. Gel use was shown to result in a 47% reduction of HIV infection. In contrast, the same adjustment for the oral TDF and FTC/TDF arm analyses did not show adequate confounding control. Moreover, no protection was shown for either of them. The difference between the gel and oral formulation results might be explained by the fact that oral administration of the drug results in a much higher plasma concentration, so that the laboratory cutoff used to discriminate between adherers and non-adherers might be suitable for gel but too low to prove continuous use of the drug for oral treatment.

"Inferring causal effect among adherers is a challenging task in randomized clinical trials. The new regression analysis strategy we proposed for assessing prevention effect among adherers suggests evidence of protection against HIV infection among gel users in the VOICE study," said Dr. Dai. The same analysis could be useful for future efficacy trials not only testing PrEP but also other prophylactic and therapeutic strategies.

Dai JY, Hendrix CW, Richardson BA, Kelly C, Marzinke M, Chirenje ZM, Marrazzo JM, Brown ER. 2015. Pharmacological Measures of Adherence and Risk of HIV Acquisition in the VOICE Study. J Infect Dis. doi: 10.1093/infdis/jiv333. [Epub ahead of print]

Supplementary information: Vermund SH, Walker AS. Use of Pharmacokinetic Data in Novel Analyses to Determine the Effect of Topical Microbicides as Preexposure Prophylaxis Against HIV infection. 2015. JID. [Epub ahead of print]