

Use of Pharmacokinetic Data in Novel Analyses to Determine the Effect of Topical Microbicides as Preexposure Prophylaxis Against HIV Infection

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(See the major article by Dai et al on pages 335–42.)

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In this issue of *The Journal of Infectious Diseases*, Dai et al reexamine the VOICE trial (MTN 003), whose primary study outcomes failed to indicate that topical tenofovir, oral tenofovir, or oral tenofovir/emtricitabine protect women against human immunodeficiency virus type 1 (HIV) infection [1]. The VOICE trial had collected extensive plasma tenofovir levels, enabling the investigators to examine protocol drug adherence with an objective measure [2]. Hence, the intent-to-treat analyses were adjusted by Dai et al, using 2 definitions based on detecting tenofovir in plasma either (1) at least once during follow-up or (2) at 3 months of follow-up [1]. For the gel arm only, analyses that adjusted for baseline predictors of HIV infection risk resulted in a reversal of the negative trial results, with an adjusted relative risk for HIV infection prevention of 0.53 (95% confidence interval, .29–.97) among

women with tenofovir ever detected and 0.40 (95% confidence interval, .16–.98) among women with tenofovir detected at 3 months, compared with women in the placebo arm. (We presume that the adjusted relative risk would be similar if nonadherent women were the comparison group, but this is not presented.) Given the ability of these adjusted models to present as-treated or per-protocol analysis with substantially reduced confounding, the conclusion of no effect was reversed, with a strong suggestion that the topical preexposure prophylaxis (PrEP) worked to protect gel users, when the gel was actually used. The biological marker was not successful in predicting nonadherence in the 2 oral drug arms.

The debate between the merits of intent-to-treat and as-treated or per-protocol analyses are familiar to clinical trials methodologists [3]. Abandoning the randomized design inherent in intent-to-treat analyses introduces potentially unmeasured confounding; in the case of oral or topical PrEP, the baseline HIV infection risk could differ between women using PrEP and women not using it. If risky behaviors or higher-risk sexual contacts were more frequent among the women who were not using the product, then the product could look efficacious, but this would really merely be a marker of lower risk exposure in the treated group. Hence, randomized clinical trials aiming to show superiority should not

rely on as-treated or per-protocol analyses except as secondary data analyses to inform future work. In contrast, for non-inferiority trials, per-protocol or as-treated analyses can be informative, even given their potential biases.

The use of a biological indicator by Dai et al as a firm measure of protocol adherence is valuable for a host of studies in which the product is being used by study participants and the administration of the product is therefore not in the control of the investigators. The VOICE study was notable for many field research insights. First, many of the women in the trial were disingenuous, stating that they were using the product when they were not. Social response bias was therefore likely, with some individuals telling the healthcare workers what they thought that the workers wanted to hear about adherence. This may have been a major factor in the motivations of VOICE trial participants. Many women feared PrEP side effects but did not want to risk alienating VOICE study staff. In addition, a desire to receive study-related remunerations may have led some women to sign up for the trial without having any firm intention of actually using the product.

Analogous concerns may have been factors in the negative results of the FEM-PrEP and the FACTS trials of topical PrEP, both of which suggested no benefit of tenofovir-based microbicide use in HIV infection prevention but had very poor adherence among participants;

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in the face of participating women choosing not to adhere to product use in high proportions, the ability of the study to address the original research question of biological efficacy was compromised [4, 5]. In contrast, women in stable couples relationships in the Partners PrEP and TDF1/TDF2 studies and at-risk women in rural South Africa in the CAPRISA 004 study had adherence rates with PrEP (oral or topical, depending upon the trial) that were high enough to demonstrate definitive efficacy [6–8]. Among men who have sex with men, several trials and observational studies demonstrated overall trial product efficacy and effectiveness [9–12]. In the context of this entire body of work [13], the findings of Dai et al are more easily interpreted: although women who adhered to PrEP may have been different from women who did not, the weight of the evidence from the VOICE trial is that the products worked to prevent HIV infection among women who used PrEP.

Whether or not subjects should be presented with their own adherence data during the trial, to motivate adherence, is debatable [1, 14, 15]. On one hand, adherence can be improved. On the other hand, transient so-called white-coat adherence may be nurtured when a subject knows that a biological sample will be obtained at the time of a visit. In the PrEP field, adherence is so critical to the biological benefits that one might advocate for monitoring and feedback for new, untested products but focus on more-practical operational research on products and interventions, including behavioral interventions to encourage adherence, whose benefits have been confirmed in the context of high adherence [16]. The value of biological surrogates for measuring treatment adherence at the trial's end, however, is indisputable. A negative trial result attributable to nonadherence has far different clinical and public health implications than a negative trial result due to failure of the product to produce the intended therapeutic or preventive effect!

The biostatistical approaches taken by Dai et al were built upon a reasonable

assumption, known as the “exclusion restriction” assumption in the causal literature. Specifically, if, among those with no pharmacological evidence of adherence, it is possible to adjust for many confounders such that their risk is indistinguishable from those on placebo, then, under specific assumptions, adjustment for these confounders should also enable the efficacy of the product in those who took it to be estimated. Dai et al showed that they could sufficiently adjust for such confounding for a tenofovir gel product but not for oral tenofovir/emtricitabine or oral tenofovir alone. Data from other studies can be used to infer that the null effect for the oral formulations after this adjustment is plausibly due to the pharmacological measure itself, that is, that the biological surrogate means something different in the oral prophylaxis groups, compared with the topical gel group. In future trials, it might not be possible to distinguish genuine lack of efficacy, even among adherers, from issues involving the use of the biological surrogate. At least to some degree, the success of the method thus relies on already knowing what answer to expect.

The future of topical PrEP is likely to be as microbicides whose adherence challenges are far less than those of current products, which require a high degree of protocol adherence. The current trials of nonnucleoside reverse-transcriptase inhibitor (NNRTI) prophylaxis use a long-acting dapivirine-containing vaginal ring that must be replaced once monthly, which, it is hoped, will be a less complex approach than daily or coitally dependent self-dosing. Two phase 3 trials are in progress, with efficacy results expected in 2016: MTN-020 (ASPIRE) and IPM 027 (The Ring Study) [17, 18]. High efficacy is hoped for, since drug resistance might be expected in breakthrough infections after NNRTI monotherapy prophylaxis. If highly efficacious, a monthly ring could be a vital preventive tool for women, more popular and deployable on a public health scale than PrEP methods for those who require more-intensive engagement,

especially in sub-Saharan African regions with the highest incidence of HIV infection [19]. (For anal sexual exposures among men or women, a depot topical ring approach is not likely to be feasible.) Statistical methods like those presented here by Dai et al may well be needed to gain the most value from ongoing studies and are most welcome in this complex HIV prevention research arena.

Note

Potential conflict of interest. Both authors: No reported conflicts. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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