Response to Invited Commentary

Murnane, Coley, and Baeten Respond to “Every Good Randomization Deserves Observation”

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We thank Westreich and Edwards for their insightful commentary (1) on our paper about estimating the efficacy of pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) prevention in a randomized trial with imperfect adherence (2). Westreich and Edwards address the important question of how we might generalize or transport efficacy estimates from study samples to real-world populations. We all agree that intention-to-treat efficacy estimates from randomized trials, despite being study-population average estimates and unbiased in their design, do not necessarily represent real-world effectiveness.

A common assumption is that persons who enroll in randomized trials are highly motivated and, barring significant side effects or other unacceptability of the intervention, will adhere to the study protocol. Results from PrEP trials have demonstrated that such protocol compliance does not always occur. Poor adherence in these trials may be attributable to qualities of the intervention itself (e.g., the burden of daily pill-taking, stigma around using medicines commonly prescribed for treatment of HIV infection) as well as the clinical trial process (e.g., uncertainty about the efficacy of an unproven product and use of placebo) (3, 4). Ultimately, adherence likely reflected participants’ personal motivation about the research question and/or their commitment to doing what researchers requested of them, perhaps more so than the real-world direct desire to prevent HIV acquisition. Indeed, the results of PrEP trials are a stark reminder regarding any intervention requiring ongoing adherence by trial subjects, including interventions for health conditions other than HIV, that intention-to-treat efficacy might significantly underestimate true biological effects and potentially real-world effects as well.

Westreich and Edwards propose that assessment of effect modifiers in both the study and target populations may inform the generalizability of results (1). Because efficacy relies on adherence to the medication regimen, adherence itself may be viewed as an effect modifier; thus, foresight about the distribution of this effect modifier (PrEP adherence) in a real-world population will aid us in estimating the effect of PrEP in that population as a whole. Identifying priority populations for PrEP is a central strategy of PrEP implementation, with a key consideration being identifying persons at higher risk who are ready to take a pill daily for HIV prevention. Prioritizing higher-risk populations will maximize the prevention impact, with fewer numbers needed to treat to treat in order to prevent 1 new infection. Adherence readiness may be subjective, but in a real-world implementation setting, PrEP would not be provided to persons who were not personally interested in a prevention strategy requiring daily adherence and would not be continued in those who did not return for medication refills. In this way, implementation of PrEP may be substantially different from clinical trials, in which investigators could not counsel participants on efficacy at enrollment (since it was unknown and placebo was used) and were obliged to follow all subjects once they had been randomized to avoid bias associated with postrandomization dropout. We might therefore consider real-world PrEP, delivered with known efficacy counseling, to be a different version of treatment than that used in randomized trials, potentially violating Hernán and VanderWeele’s third condition of transportability (5).

We are encouraged by recently reported data from 2 open-label studies of PrEP implementation for HIV prevention in different geographic and at-risk settings: the Partners Demonstration Project, carried out among high-risk HIV-serodiscordant couples in East Africa (6), and the PROUD Study (‘‘Pre-Exposure Option for Reducing HIV in the UK: Immediate or Deferred’’), conducted among high-risk men who have sex with men in the United Kingdom (7). In both studies, HIV protection effectiveness was extremely high (96% for the Partners Demonstration Project and 86% for PROUD), outpacing the efficacy estimates from the clinical trials done in similar at-risk populations. More studies of PrEP implementation, including identification of successful strategies for identifying high-risk populations that are motivated to high adherence, will determine the public health impact of this new prevention intervention.
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REFERENCES


