

FROM ENGAGEMENT TO LEADERSHIP: PLACING COMMUNITY PRIORITIES AT THE HEART OF HIV PREVENTION RESEARCH

By Jeremiah Johnson

Highly Effective PrEP Requires Rethinking HIV Prevention Trial Design

The advent of effective biomedical prevention options has introduced a number of ethical tensions in the field of HIV prevention research. While the development of a safe, highly effective pre-exposure prophylaxis (PrEP) using the drug combination TDF/FTC (tenofovir disoproxil fumarate and emtricitabine) is welcome, we need more biomedical prevention tools. As we've learned from the field of contraception, options are important, and we are unlikely to achieve a sustainable end to HIV without a vaccine.

In any field of clinical research, ethics can become more complicated once one or more highly effective interventions are developed. The use of a placebo in the control arm is only acceptable if we can reasonably say that nothing better exists, otherwise the ethical obligation is to provide the standard of care or, in this case, the standard of prevention (SoP). The principle of equipoise in research ethics requires the investigator to be genuinely unsure as to whether participants in the experimental arm will see as much benefit as those in the control; the better the control intervention is, the harder that bar is to clear. And if the SoP is extremely effective and safe, ethics may suggest it should be given in both arms, with the new intervention added on top of the background SoP in the experimental arm. But because clinical trials must be powered to detect differences in events (e.g., HIV infections) in the control and experimental arms, the stronger the SoP is, the larger or longer the trial must be to pick up enough endpoints to detect a difference in efficacy. Larger trials are more expensive and can greatly slow down research.

While the pre-PrEP prevention toolbox did contain effective interventions, low adherence to control arm options such

as condoms and behavioral counseling effectively ensured that researchers would see a difference in HIV infections if a new prevention modality was effective at averting infections. But PrEP changed the game: It is both highly efficacious and easier for more people to adhere to. As such, the ethical

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obligation to offer trial participants the current best biomedical prevention option, TDF/FTC PrEP, now stands in conflict with the traditional pathway for developing new technologies. As additional effective tools are approved, such as long-acting injectable PrEP and vaginal rings, these challenges will be even more pronounced.

Seeking Community Input on a Way Forward

In November 2018, the major HIV prevention trial networks funded by the National Institutes of Health invited community advocates, including TAG, to take part in a symposium on future HIV prevention trial designs in the post-PrEP era.

The stakeholders in the room weighed several ethical considerations: What is the most ethical control arm or background SoP for new prevention trials? Can we develop trial designs that allow us to enroll participants who are not using other forms of biomedical prevention as part of a control arm? Are there alternative ways to demonstrate efficacy, in addition to measuring new HIV infections?

While input at the gathering helped to advance the dialogue, there were few definitive answers to these questions. In many ways, the discussion highlighted that the way forward must be just as focused on finding the right process for resolving ethical tensions as finding the right answers—and that community leadership must always be at the heart of that “right process.”

Community Priorities for Future Prevention Clinical Trials

As discussions advance regarding novel approaches to establish efficacy for new HIV prevention tools, major community concerns are likely to fall into at least three “buckets”:

Bucket One: Providing Quality Access to Existing Prevention Tools

A major concern for community research advocates going forward will be the SoP offered to participants as part of future clinical trials. TAG took a deep dive into this topic in 2017 by surveying community research advocates and members of community advisory boards, finding a clear preference for easy access to PrEP for participants whenever possible and that all trial participants should receive comprehensive education on PrEP and referrals to PrEP services, if interested (see: [HIV Research in the Era of PrEP: The Implications of TDF/FTC for Biomedical Prevention Trials](#)).¹ But many respondents noted that these aren’t easy questions. Ultimately, advocates from communities hosting HIV prevention research need to be involved by providing guidance on how to choose an acceptable background level of prevention support in a trial while advancing vaccine, microbicide, and other essential research.

Bucket Two: Clearly Establishing the Risks and Benefits of Novel Statistical Approaches or the Use of Correlates to Estimate Efficacy

Researchers are investigating alternative ways of establishing efficacy in cases where participants receive a highly effective

SoP package and are unlikely to have new HIV infections. In one approach under exploration, bacterial sexually transmitted infections (STIs) are being viewed as a proxy to estimate the number of HIV infections averted in a clinical trial. Another method might be to use historical incidence data to create an external control arm. The idea behind both is to estimate how many participants would have gotten HIV in the absence of effective prevention options, to sidestep the ethical issues around SoP provision. At this year’s Conference on Retroviruses and Opportunistic Infections, investigators from the Discover trial—which was designed to determine if F/TAF (emtricitabine and tenofovir alafenamide) is non-inferior (as opposed to superior) to TDF/FTC as PrEP—in partnership with the Centers for Disease Control and Prevention gave a glimpse into what this might look like, revealing a model using background incidence in the communities where research took place to estimate what percentage of infections had been averted.²

But the issue with these methodologies is that bacterial STIs and incidence estimates are highly variable in different contexts and within different populations. Given that STI infections are rising around the globe and HIV incidence is in fluctuation, we’re basing our estimates on a moving, inconsistent target. Community advocates will understandably be concerned with the risks of overestimating or underestimating efficacy with these approaches. As novel ways of proving efficacy are developed, it will be essential for researchers and statisticians to clearly explain the dangers (and benefits) of these new approaches to community advocates and to solicit explicit guidance on when these new methodologies are appropriate to use.

Bucket Three: Ensuring Ethical Enrollment

Researchers are also evaluating whether there are novel recruitment methods that could allow for a placebo-controlled randomized controlled trial (RCT) in which participants include people who cannot or will not use PrEP. One such way to do this would be to recruit individuals and establish their level of interest in PrEP use. Those who are already on PrEP or who would like assistance in getting on PrEP would be placed within an observational cohort, while those who are not interested in PrEP would be randomized into an experimental or control arm. If individuals in the observational cohort go off of PrEP, they too could become part of the RCT; similarly, individuals in the RCT who want to go on PrEP would switch into the observational cohort.

Proposals to Modify Population Enrolled: Addressing the Remaining Unmet Need

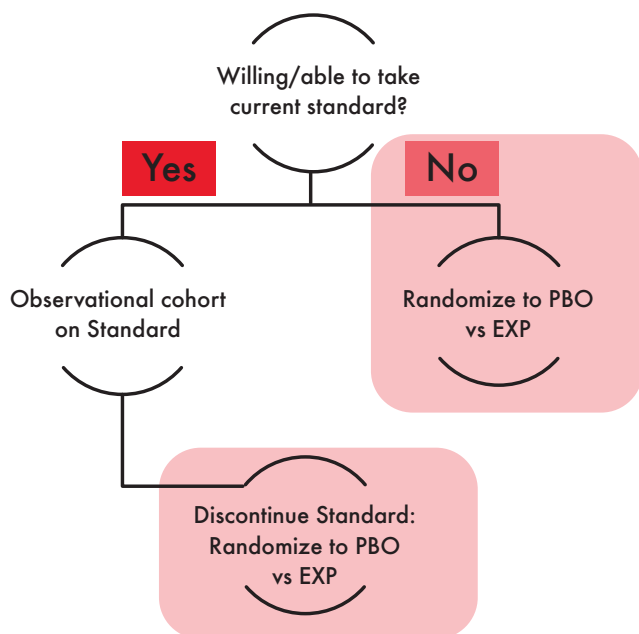


Image adapted from: Donnell D. Novel trial design in the era of successful HIV prevention interventions. Presented at: 3rd HIV Research for Prevention conference; 2018 October 21-25; Madrid, Spain.

On the surface, the approach is appealing; it provides for participant autonomy while allowing for a placebo-controlled RCT. And many community advocates, including those of us at TAG, are interested in pursuing this option in order to facilitate development of future prevention tools. However, many challenges exist in this approach. What are the risks of selection bias between the observational and RCT cohorts, and how would researchers minimize incorrect conclusions? How would researchers ensure that the trial wouldn't disrupt successful PrEP use by potential participants? How would

we monitor that researchers are appropriately offering PrEP, including adherence and access support, to those in the observational cohort?

As such, it becomes once again imperative that the dangers and benefits of this approach are clearly presented to community advocates in order to draw from their expertise on what will and will not be acceptable for future research.

With all three "buckets," concrete answers are few; however, one consistent conclusion stands out: Community leadership in navigating these ethical minefields will be essential. Given the highly technical aspects of these discussions, establishing that sort of community leadership will require dedication from researchers and trial networks; simple attempts at "engagement" will fall short. Community research advocates will need funding to develop and share their expertise, while researchers and trial networks will have to provide education and regularly solicit feedback from community advisory boards and the communities where research takes place. Additionally, researchers may need to make difficult decisions in order to meet the needs of community members, both with regard to the challenges outlined in this article and many other priorities that are of concern to community advocates, such as greater inclusion of vulnerable populations in research and real-world access to the products that result from the hard work of research communities.

Endnotes

1. Jefferys R, Johnson J, Horn T. HIV Research in the Era of PrEP: The Implications of TDF/FTC for Biomedical Prevention Trials. New York: Treatment Action Group; 2017. <http://www.treatmentactiongroup.org/users/hiv-prep-prevention-trials>
2. Hare C, et al. The phase 3 Discover study: daily F/TAF or F/TDF for HIV preexposure prophylaxis (Abstract 104). Poster presented at: 26th Conference on Retroviruses and Opportunistic Infections; 2019 March 4-7; Seattle, WA. <http://www.croiconference.org/sessions/phase-3-discover-study-daily-ftaf-or-ftdf-hiv-preexposure-prophylaxis>