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Perspective

Where Were the Women? Gender Parity in Clinical Trials

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In 2017, a total of 19% of all new HIV infections in the United States and nearly half of infections globally were in cisgender (nontransgender) women. Women of childbearing potential shoulder a disproportionate burden, which raises further concerns about perinatal transmission of the virus. Preexposure prophylaxis — pharmacologic prevention of HIV acquisition with coformulated tenofovir disoproxil fumarate and emtricitabine (F/TDF) — has been shown to be effective in women, was approved by the Food and Drug Administration (FDA) in 2012 for women and men, and is a cornerstone of the national strategy for Ending the HIV Epidemic.

Coformulated tenofovir alafenamide and emtricitabine (F/TAF) is a sister prodrug of F/TDF that has the potential to cause less loss of bone mineral density and fewer renal toxic effects than F/TDF. A new drug application for F/TAF for the treatment of HIV infection in men and women was submitted to the FDA in April 2015 and approved in April 2016. The FDA reviewed a substantial amount of safety and efficacy data for F/TAF, as it does for all new medications, and confirmed that the supporting studies met its established criteria for statistical rigor, pharmacologic standards, and inclusion of diverse populations.

Two months after its approval for treatment, F/TAF's manufacturer, Gilead Sciences, moved forward with an effort to expand the drug's indications to include prevention of HIV infection. To do so, they collaborated with researchers, community members, and the FDA to develop a new preexposure prophylaxis trial protocol — the DISCOVER trial — and to work toward a supplemental new drug application for F/TAF. Designed as a noninferiority trial, DISCOVER compared F/TDF with F/TAF in more than 5000 men who have sex with men and 74 transgender women who have sex with men to evaluate the efficacy and safety of F/TAF when used for prevention. The trial specifically excluded cisgender women because of perceived challenges in enrollment and concern about reaching a meaningful end point. DISCOVER was registered with and posted to ClinicalTrials.gov (NCT02842086) in June 2016.

The requirements for a supplemental new drug application are similar to those for a drug's initial new drug application, and the new application is subjected to the same scientific and ethical standards. These include the FDA Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, which "requires sponsors to include a fair representation of both genders as participants in clinical trials so that clinically significant gender-related differences in response can be detected."[1] The guidance also specifies that trial

participants must be representative of the patient population likely to be prescribed the drug once it is approved and that data must be presented for each relevant subgroup.[1]

In March 2019, the manufacturer reported in abstract form the initial efficacy and safety data from the DISCOVER trial. Despite the few new HIV infections that occurred during the study, F/TAF was found to be noninferior to F/TDF, with a similar adverse-event profile. Serum creatinine levels were significantly different between the two groups, although the difference probably did not carry any clinical significance: F/TAF resulted in a change of 0.01 mg per deciliter and F/TDF a change of 0.02 mg per deciliter.[2]

On August 7, 2019, the Antimicrobial Drugs Advisory Committee of the FDA discussed the recently reported and unpublished data from DISCOVER. They also reviewed the previously published pharmacokinetic data on F/TAF that demonstrated similar systemic levels of F/TAF in men and women with daily dosing of the medication.[2] At the time of consideration, and nearly 3 years after the public notification of the launch of the DISCOVER Trial, no trial was actively examining (or had yet examined) F/TAF for use as preexposure prophylaxis in cisgender women. The committee acknowledged that differences in drug levels between rectal and vaginal mucosa may affect overall efficacy in HIV prevention and voted 16 to 2 for approval of F/TAF in men who have sex with men and transgender women and 8 to 10 against approval in cisgender women.[3] Scientists and community advocates on the panel recognized the consequences of this decision, which was dictated by the inadequacy of prevention data for women, and were keenly aware of the impact the disapproval would have on access for cisgender women. The committee chair conveyed this frustration, saying, "We've failed women." Ultimately, on October 3, 2019, the FDA approved F/TAF for HIV prevention in at-risk "adults and adolescents," but "excluding those who have receptive vaginal sex."[4]

This controversial story highlights numerous flaws in the drug-approval process. From the time the trial was first registered with ClinicalTrials.gov in 2016, through the approval of the protocol by human-subjects committees at 94 clinical sites, to the submission of a supplemental new drug application to the FDA with review by the Antimicrobial Drugs Advisory Committee in August 2019 and then final approval by the FDA, it was evident that the submission would never meet the gender-specific standards set forth by the FDA's own guidance.

Equity and inclusion in clinical trial design are essential to scientific advancement, ensuring that the benefits of innovation and drug discovery safely reach everyone in need. Historically, women — especially those who were pregnant or had childbearing potential — were often considered a vulnerable population and therefore excluded from clinical trials; this practice limited our understanding of women's health and the potential for diverse pharmacologic responses. The FDA's Office of Good Clinical Practice first called for representation of all genders in clinical trials in 1993, simultaneously acknowledging that human-subjects committees should include these standards in their evaluation of protocols and surveillance of research.[1]

There are limited evidence-based reasons for excluding people from trials on the basis of gender. Just this year, the FDA posted draft guidelines on the inclusion of men in studies of new breast-cancer therapeutics, citing prior exclusion as a barrier to effective treatment options. Men account for less than 1% of all breast-cancer cases, but under these guidelines, the "FDA does not intend to consider low expected accrual rates of male patients with breast cancer to be a sufficient scientific rationale for excluding them from a clinical trial."[5] Meanwhile, in the same month these guidelines were published, the FDA advisory committee reviewed data on F/TAF for HIV prevention that intentionally excluded women — a population that accounts for nearly 20% of all new HIV infections in the United States and 46% of all infections globally. The manufacturer justified its decision by citing difficulty in identifying "a relevant female cohort."[2]

The responsibility for the exclusion of women in the design of the DISCOVER trial and the gender-specific approval of F/TAF for HIV prevention rests on all of us. Clinical trial design requires diverse voices and intentional inclusion criteria. It is up to human-subjects committees to maintain vigilant oversight of study protocols with these FDA standards in mind, regardless of whether the studies in question are industry-sponsored. And when the FDA is presented with data that exclude half the world's population, it can use the tools at its disposal to address the violation.

The current approval of F/TAF that excludes "those who have receptive vaginal sex" establishes a two-tier system in which men may be prescribed the medication

with insurance approval, whereas women may receive it only off-label, in the absence of data, and without insurance coverage. The path forward should be clear: a well-designed, rapidly enrolled, robust clinical trial of efficacy in cisgender women is urgently needed.

In granting approval for the drug's expanded indication, the FDA obligated the manufacturer to study the drug in cisgender women. In response, the company plans to undertake a limited study in 1500 women in sub-Saharan Africa focused on safety and noninferiority that is scheduled to begin enrollment by 2020. In short, a study involving women that was deemed infeasible in 2016 is finally being considered. The backlash from the scientific, global, and advocacy communities against the FDA's limited approval of F/TAF suggests that they expected and deserved better; they are all watching for remediation. The responsibility now lies with the FDA and the scientific community to enforce the rapid completion and reporting of this study in women and, in the process, to work to revise the current regulations and drug-approval process to truly require equity and inclusion.

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