EDITORIAL

The Real PURPOSE of PrEP — Effectiveness, Not Efficacy

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Given the 40 years of research and the wealth of successful tools that have been developed to prevent, diagnose, treat, and suppress human immunodeficiency virus (HIV) infection, how is it possible that in 2024 the incidence of HIV type 1 (HIV-1) infection is more than 3.5 per 100 person-years among young women in southern Africa?[1] The efficacy of preexposure prophylaxis (PrEP) to prevent HIV infection was first shown in 2010 in the landmark Preexposure Prophylaxis Initiative (iPrEx) trial of emtricitabine–tenofovir disoproxil fumarate (F/TDF), largely in men who have sex with men (MSM).[2] In July 2012, the time of Food and Drug Administration approval of F/TDF for HIV-1 PrEP in MSM, heated discussion ensued about whether these findings might be extrapolated to support PrEP use in other high-risk populations, such as cisgender women.

Bekker et al.[1] now report in the *Journal* the results of a well-done, large, randomized, controlled trial in South Africa and Uganda of PrEP for cisgender women (PURPOSE 1). Participants were assigned in a 2:2:1 ratio to receive twice-yearly subcutaneous lenacapavir (an HIV-1 capsid inhibitor), daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral F/TDF (active control). Given that inclusion of a placebo group was considered to be unethical, the trial also included screened but unenrolled persons as a no-PrEP observational group.

The background HIV incidence in the no-PrEP group sadly mirrored previous estimates, at 2.41 per 100 person-years. Of the 55 incident infections among participants in the three intervention groups, there were none in the lenacapavir group, 39 in the F/TAF group, and 16 in the F/TDF group, with an incidence of 0, 2.02, and 1.69 per 100 person-years, respectively. This efficacy exceeded the predefined stopping criteria, and the trial was stopped early. Meta-analyses have previously shown a dose-responsive PrEP efficacy, depending on adherence.[3] Although it is always challenging to fully understand a postrandomization assessment, because medication adherence and other behaviors may track together, the PURPOSE 1 trial corroborates these gradient findings. Nevertheless, adherence and active drug at the time and site of HIV-1 exposure are probably both important for effective prevention. Findings from the PURPOSE 1 trial underscore the challenges of adherence to a daily oral medication, and the incidence of HIV-1 infection was no different from background incidence when documented adherence was low. With approximately 92% attendance for the twice-yearly lenacapavir injections, the PURPOSE 1 trial exemplifies not only that women can dependably adhere to this administration schedule but also that levels of an HIV-1 capsid inhibitor can remain high enough over a period of 6 months to reliably prevent infection.

The results of the PURPOSE 1 trial will raise scientific questions. For example, how can we address the diagnostic challenges of rare acute HIV-1 infection (as shown in the cabotegravir PrEP studies also now reported in the *Journal*[4])? What are the best tactics to combat the large number of concomitant sexually transmitted infections? What is the potential for emergent viral resistance? How do these data inform potential use for other groups at high risk for HIV infection? And how can we improve contraceptive options for women at high risk for HIV infection. Given the high pregnancy rate among

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participants in the PURPOSE 1 trial, assessment of the safety of lenacapavir in pregnancy is a priority. Perhaps, however, the most critical question is how — more than a decade after PrEP was first approved in the United States and several years after the promising DISCOVER results among MSM[5] — we have failed women at high risk for HIV infection for so long.

A key challenge to decreasing the incidence of HIV infection is identifying high-risk populations (especially women), engaging them, and providing them easy, low-barrier, and low-cost access to a PrEP regimen that works and to which they can adhere. Because previous PrEP regimens have proven to be highly effective when taken as prescribed, the PURPOSE 1 trial uniquely addresses only the last among these hurdles.

South Africa, the primary country of enrollment in the PURPOSE 1 trial, updated its PrEP guidelines in 2021, endorsing PrEP use for persons at greatest risk for HIV infection, including adolescent girls and young women as well as MSM, among others.[6] Demographic data for South Africa suggest there are approximately 4.5 million adolescent girls and young women between the ages of 16 and 25 years (PURPOSE 1 enrollment criterion), and the Joint United Nations Program on HIV/AIDS estimates an additional 750,000 South Africans among PrEP-eligible key populations.[7] With more than 5.25 million eligible South Africans, as of 2021 a mere 350,000 (<7%) had ever received a PrEP prescription; durable use is probably far lower.

Reported barriers to PrEP use among young persons in the African context include social stigma, fear of side effects, long travel or wait times for appointments, inconvenient clinical operating hours, and drug costs.[8] To bridge the current canyon between PrEP efficacy and effectiveness, future efforts must address these challenges. To start, PrEP drugs proven to work should be financially accessible to the populations in the countries studied. F/TDF is available in South Africa for less than $50 per year. Meanwhile, lenacapavir currently costs approximately $43,000 annually in the United States, according to Red Book Online (Truven Health Analytics), and access to lenacapavir in South Africa is severely limited. But, the results of the PURPOSE 1 trial have now created a moral imperative to make lenacapavir broadly accessible and affordable as PrEP to persons who were enrolled, as well as all those who are similarly eligible and could benefit.[9]

So now we have a PrEP product with high efficacy. That is great news for science but not (yet) great for women. Now, the imperative is to spend time, resources, and political will on access, implementation, and delivery. And that plan must include a mechanism to finance these drugs so that the women who have borne an unacceptably high HIV infection burden and who have volunteered for decades in studies of HIV prevention can reap the PrEP benefits and remain HIV free.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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