Editorial

Working at Cross-PURPOSEs to Ending HIV

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Almost 15 years ago, the results of the Preexposure Prophylaxis Initiative (iPrEx) trial, which showed the efficacy of oral antiretroviral agents as preexposure prophylaxis (PrEP), were reported in the *Journal*.[1] However, only 15% of persons who would benefit from PrEP currently receive it.[2] The recent modest fall in the global incidence of human immunodeficiency virus (HIV) infection obscures the ongoing epidemic among key populations in high-income, middle-income, and low-income countries, including continued high infection rates among young women in southern Africa. The United Nations 2030 prevention targets will not be met unless something different is done, and soon.

The results of the PURPOSE 2 trial, reported by Kelley et al. in this issue of the *Journal*[3] essentially mirror those of the PURPOSE 1 trial, which was conducted in Uganda and South Africa. The PURPOSE 1 trial showed near-total protection from HIV infection among participants who received subcutaneous lenacapavir every 6 months.[4]

The PURPOSE 2 trial, which was conducted in the United States and six middle-income countries (Mexico, Argentina, Brazil, Thailand, Peru, and South Africa), recruited cisgender men and gender-diverse persons who were having condomless receptive anal sex with partners assigned male at birth. Recreational drug use and sexually transmitted infections (STIs) were common in the screened population.

Participants underwent randomization in a 2:1 ratio and were assigned to receive lenacapavir every 26 weeks or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF). The incidence of HIV infection in the trial population was compared with the background incidence in the screened population.

The incidence of HIV infection was lower in the lenacapavir group than in the F/TDF group: of the 11 incident infections, 2 occurred in the lenacapavir group (0.10 per 100 person-years) and 9 occurred in the F/TDF group (0.93 per 100 person-years). The background incidence of HIV infection in the screened population was 2.37 per 100 person-years. The adherence to oral PrEP and the efficacy of PrEP were substantially higher in the PURPOSE 2 trial than in the PURPOSE 1 trial.

The two participants in the lenacapavir group who acquired HIV infection in the current trial had active STIs. Neither participant reported symptoms of HIV infection. The participants had presumed effective lenacapavir levels, and both participants were found to have the capsid

inhibitor mutation N74D, indicating that long-term resistance monitoring for breakthrough cases is warranted. This finding has potential implications for treatment options under development.

The nine HIV infections in the F/TDF group were associated with low or undetectable levels of tenofovir (in eight participants) or discontinuation of the trial drug (in one participant). Drug monitoring suggested steadily decreasing adherence over time across this group.

The near-total protection shown in the PURPOSE 1 and 2 trials is catalytic for HIV prevention. The long-acting injectable nature of lenacapavir addresses the major Achilles heel of oral PrEP: adherence. There is much to praise about these trials: the designs involved substantial community participation and used background HIV infection as the counterfactual control; recruitment was performed in populations that are disproportionately affected by HIV and have previously been underrepresented in pharmaceutical trials, and social harms were addressed at screening and throughout the trials; and the participants could continue taking lenacapavir after the trial.[5] The safety profile appeared to be acceptable, and the PURPOSE 1 trial provides important safety data with respect to pregnancy.

But all is not well in the PrEP field. Cabotegravir, another long-acting injectable PrEP that was shown to be effective in 2020, was licensed by the Food and Drug Administration 3 years ago, but only a tiny number of people receive it globally. ViiV Healthcare, the originator, licensed the medication after a lengthy process and civil society pressure to three generic manufacturers through the Medicines Patent Pool (MPP), with scale-up only projected for late 2027.[6] In South Africa, where almost 20% of the global population of persons with HIV live, less than 5000 people take cabotegravir PrEP, even 2 years after local registration. ViiV, the only supplier of cabotegravir, charges almost $24,000 (in U.S. dollars) per year in wealthy countries, with an "access" price of $180 per year for selected countries.[5] A price of $9 to $15 per injection for cabotegravir is required to make the drug as cost effective as oral PrEP.[7] Preliminary modeling suggests that lenacapavir's longer half-life and the fewer required visits would allow South Africa to attain 2030 prevention targets faster than with cabotegravir.

Gilead Sciences has issued lenacapavir manufacturing licenses to only six generics companies, bypassing the MPP access process, and excluding most countries where the PURPOSE 2 trial was conducted (including the Americas), where HIV incidence is concerning; these countries are unlikely to be able to afford the price tag of $42,000 per year. Estimates suggest that the drug can be made profitably for $100.[7,8] Gilead announced that it will supply all required lenacapavir at "no profit" until generics are available, anticipated in 2028, but gave no price.[5] The license includes troubling and complex legal language regarding access to the active pharmaceutical ingredient, importation and packaging restrictions, and "anti-diversion" clauses with onerous reporting requirements.[9]

A drug innovation this powerful that could change the trajectory of an epidemic should compel urgency. PrEP uptake has been so poor that immediate and creative government, agency, and donor focus is required. Injections need to be made available swiftly to inform program design so that the tens of millions of people who would benefit from PrEP can access it.

Currently, pharmaceutical companies are consigning an entire generation of people to lifelong infection and treatment, in a macabre slow dance around price and patents. They should be heroes for developing these innovations and allies in immediate access, not the villains in yet another tragic piece of HIV history.

References

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