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Perspective

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An HIV Vaccine in the Era of Twice-Yearly Lenacapavir for PrEP — Essential or Irrelevant?

Lauren P. Jatt, M.D.,[1] Nyaradzo M. Mgodi, M.B., Ch.B., M.Med.,[2] Susan P. Buchbinder, M.D.,[3] Glenda E. Gray, M.B., Ch.B.,[4] and James G. Kublin, M.D., M.P.H.[5]

In November 2024, results from the PURPOSE 2 trial — a large, randomized, phase 3 trial evaluating the efficacy of twice-yearly lenacapavir injections for HIV prevention in cisgender men and gender-diverse persons — were published, revealing that the incidence of HIV infection among people who received lenacapavir was 89% lower than the incidence among people who received daily oral emtricitabine–tenofovir disoproxil fumarate and 96% lower than the background HIV incidence.[1] These findings followed the results of the PURPOSE 1 trial, which showed that twice-yearly lenacapavir provided complete (100%) protection against HIV infection in cisgender women.[2] The discovery of a highly efficacious option for HIV preexposure prophylaxis (PrEP) that requires only twice-yearly administration has led to the question of whether a vaccine is still necessary to end the global HIV epidemic.

Twice-yearly lenacapavir shares important features with an ideal HIV vaccine: it is safe and highly efficacious for preventing HIV. The efficacy observed in the PURPOSE trials is similar to, if not greater than, that of many conventionally available vaccines. Lenacapavir is also thermostable and can be shipped and stored at room temperature, an important advantage over most HIV vaccine candidates. But the most obvious advantage of lenacapavir for PrEP is that it is not hypothetical — it is available now. Nonetheless, an HIV-prevention strategy that relied exclusively on lenacapavir would have several limitations. We therefore believe that the development of an HIV vaccine is still an essential component of the global, multipronged strategy that is needed for ending the HIV epidemic.

Lenacapavir provides shorter-lasting protection than most vaccines. People must get injections every 6 months to remain protected and must continually self-identify as having a high likelihood of HIV exposure and acquisition; there have been numerous reports of HIV acquisition in people who stopped using PrEP because their behavior changed and they thought they no longer needed it. A fairly short duration of protection also means that people must have high levels of health care engagement and adherence

to treatment. Furthermore, they must have stable access to the health care system; if they lose access because of factors such as economic hardship, war, or environmental disaster, they will be left unprotected. Durable immune responses are a key advantage of vaccines.

Another important difference between vaccines and twice-yearly PrEP is that vaccines are typically given universally, whereas PrEP services are focused on people in high-seroincidence groups. There are disadvantages to relying exclusively on interventions directed at specific populations. In eastern and southern Africa, for example, it's estimated that approximately 40% of people who become infected with HIV hadn't met the criteria for PrEP use before infection.[3] People who do meet the criteria may be overlooked by their clinicians because of bias. Population-specific interventions can also be more susceptible to the effects of stigma than universal interventions such as vaccination.

Universal administration of PrEP, although theoretically possible, hasn't been pursued in any country, given substantial barriers related to cost, adherence, and implementation. In some populations, stigmatization of PrEP use has had implications for initiation and continued use. Having a choice of HIV-prevention method is important; not everyone will choose a subcutaneous PrEP injection that sometimes leaves a visible nodule. Interventions that can be rolled out regardless of self-perceived risk are essential (although not necessarily sufficient) for preventing all new cases of HIV — not just some of them.

In addition, many low- and middle-income settings lack the robust public health infrastructure needed for administering injectable PrEP. Effectively implementing injectable PrEP programs at scale will require substantial investment, including training in administration of subcutaneous injections, which can be painful if they aren't delivered according to protocol. By comparison, every country has experience with routine immunization. Although imperfect, routine immunization systems have introduced vaccines and provided services to marginalized populations for decades.

Since lenacapavir is a small-molecule drug, its efficacy could be limited by drug–drug interactions. Lenacapavir use with strong CYP3A inducers is contraindicated because concurrent use can result in lower plasma concentrations and reduced efficacy of lenacapavir. Simultaneous use of some medications — including anticonvulsants, antimycobacterial agents, and systemic glucocorticoids — was prohibited in the PURPOSE trials.

Drug resistance is another area of concern. In the PURPOSE 2 trial, there were two cases of HIV infection in the lenacapavir group; both participants had the N74D capsid inhibitor resistance mutation at diagnosis, which suggests that lenacapavir monotherapy during the trial led to the emergence of capsid resistance.[1] Lenacapavir concentrations in both participants were in the expected therapeutic range for the trial. It's also unknown whether low-level exposure to lenacapavir after discontinuation — a result of the drug's long half-life — might lead to the emergence of resistance in some people who stop receiving injections. The emergence of HIV strains resistant to lenacapavir would render HIV-prevention programs relying exclusively on lenacapavir for PrEP ineffective.

To end the HIV epidemic, our prevention tools must be affordable, acceptable, and accessible globally. The cost of twice-yearly injectable PrEP is unknown. Other long-acting injectables for PrEP are currently unavailable or cost-prohibitive in most countries. Studies have consistently predicted that an HIV vaccine would be cost-effective.[4] An analysis comparing the cost-effectiveness of twice-yearly injectable PrEP, a hypothetical HIV vaccine, and a combination of the two products is needed.

Among the more than 4300 participants in the lenacapavir groups in the PURPOSE trials, there were only two incident cases of HIV. This near-elimination of new HIV infections is an enormous achievement. It has also led to legitimate concerns about the ability to conduct adequately powered phase 3 vaccine trials because of what many clinical trialists consider an ethical imperative to offer PrEP to anyone who would be participating in an HIV vaccine trial.

Given the numerous potential benefits of an HIV vaccine and recent progress toward achieving the induction of broadly neutralizing antibodies by means of vaccination,[5] promising vaccine candidates merit testing in large efficacy trials. One option would be to enroll only participants who decline PrEP after being linked to HIV-prevention services. The feasibility of this strategy was recently demonstrated in the Mosaico trial, which enrolled 3800 people who had declined PrEP. In addition to receiving counseling and being offered PrEP services at the beginning of the trial, participants could start using PrEP

at any point during the trial. (This trial was discontinued after an independent review found no evidence of reduced risk of HIV infection among participants receiving the investigational vaccine.) Community engagement and ethical oversight will be critical to developing acceptable trial designs.

We share the widespread enthusiasm about the potential for long-acting injectable PrEP to dramatically reduce the number of new HIV infections. We also recognize that the development of an affordable and highly effective HIV vaccine that generates a durable immune response will be rife with challenges. Although recent progress toward inducing broadly neutralizing antibodies with vaccination has brought renewed hope to these efforts, the failure of numerous previous vaccine candidates is a stark reminder of the difficulty of this endeavor.

An audio interview with Lauren Jatt is available at NEJM.org

The existence of an injectable form of PrEP that requires only twice-yearly administration raises the bar for a future HIV vaccine: it must generate a long-lasting immune response and must be cost-effective as compared with existing prevention options, and implementing it for broad population use must be more feasible than adopting widespread PrEP administration. Given the complementarity of twice-yearly injectable PrEP and an ideal HIV vaccine, we believe that only an approach that combines these interventions will end the HIV epidemic.

Disclosure forms provided by the authors are available at NEJM.org.

[1] Division of Allergy and Infectious Disease, University of Washington, Seattle; [2] University of Zimbabwe Clinical Trials Research Centre, Harare; [3] San Francisco Department of Public Health, San Francisco; [4] Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg; [5] Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle.

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Clearing the Smoke on Fossil Fuels — The Health Imperative for a Countermarketing Campaign

Linda Rudolph, M.D., M.P.H.,[1] and Vishnu Laalitha Surapaneni, M.D., M.P.H.[2]

Fossil-fuel pollution causes immediate, direct, and extensive long-term harms to human health and, as the dominant cause of climate change, threatens the ecosystems on which human survival depends. For decades, the fossil-fuel industry has obstructed efforts to curtail pollution from its products. Yet the health community has not yet deployed the communication strategies that have proven effective in fighting other health-harming industries, most notably the tobacco industry.

Each year, an estimated 5 million to 8.7 million people globally, including as many as 350,000 in the United States, die prematurely because of air pollution from combustion of coal, oil, and gas.[1] Fossil-fuel pollution is associated with asthma and other respiratory diseases, heart disease, stroke, lung cancer and other cancers, effects on brain development and neurocognitive function, and premature births and low birth weight. Moreover, the health harms of fossil-fuel pollution and climate change disproportionately affect marginalized groups both globally and within the United States. Limiting fossil-fuel combustion could prevent more than 53,000 premature deaths and provide more than $600 billion in benefits from avoided illness and deaths.[2]

International Energy Agency analyses show that expected growth in global electricity demand can be met without any new fossil-fuel extraction; a recent comprehensive analysis concludes that there is a "large consensus" across all published studies that developing new