

Long-Acting Injectable Preexposure Prophylaxis for HIV Prevention in South Africa: Is There a Will and a Way?

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Human immunodeficiency virus (HIV) antiretroviral therapy (ART) use results in substantial improvements in HIV-related morbidity and mortality [1, 2] and leads to dramatic reductions in sexual transmission of HIV among heterosexual serodiscordant couples when ART suppresses HIV viremia in the infected partner [3]. Yet 6000 new HIV infections continue to occur daily across the globe. Use of oral antiretrovirals as chemoprophylaxis has substantial potency for HIV prevention among diverse populations [4–8]. However, effectiveness is highly dependent on consistent daily or near-daily product use. For women, even more-rigorous adherence may be necessary to realize optimal protection [9], a finding borne out by complete abrogation of effectiveness when either oral or topical vaginal preparations are used infrequently [10, 11].

Long-acting injectable antiretroviral (ARV) preparations, ideally administered bimonthly or quarterly, have the potential to obviate the need for daily dosing, thereby improving adherence during exposure events, and, in theory, maximizing reductions in HIV infection incidence. In this issue of *The Journal of Infectious Diseases*, Walensky et al provide important additional context for the advent of long-acting injectable preexposure prophylaxis (PrEP). Although the medica-

tion costs after approval of these agents are unknown, the authors present a well-considered modeling exercise of the type we have come to expect from the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) group, demonstrating potential advantages and costs, as well as cost-effectiveness thresholds for the use of long-acting injectable PrEP for young South African women. This work builds on previous studies by the same authors that evaluated daily oral PrEP in a similar theoretical cohort [12].

The authors propose a base case rooted in an almost unthinkable high-incidence population, in which the cumulative lifetime probability of HIV acquisition is >60%. Initially, looking at use during the 18–25 years of age timeframe, the CEPAC model predicts substantial improvements in cumulative lifetime risk of HIV acquisition and life expectancy, compared with no PrEP, and an incremental improvement over standard daily oral PrEP. Similarly, the incidence of HIV infections and HIV-related deaths during the 5-year period of treatment are reduced incrementally, compared with standard PrEP. Both standard PrEP and long-acting PrEP are cost saving in this scenario, with long-acting PrEP costing an incremental \$150 per year of life saved, compared with standard PrEP. Fascinatingly, despite initial higher up-front financial investment costs for programmatic scale-up, in the long-run (after approximately 30 years), long-acting PrEP actually is the most cost-saving intervention, driven by overall reduced HIV infection incidence and HIV treatment and care costs. It would be interesting to re-model the cost-effectiveness of standard PrEP

and long-acting PrEP after considering the lifetime postseroconversion costs of ART implied by the new World Health Organization guidelines that recommend ART for all who are HIV infected, although such guidelines will likely only increase the cost efficiency of any HIV prevention intervention, including all PrEP modalities.

Importantly, extensive sensitivity analyses demonstrate the robustness of the findings against the obligate assumptions intrinsic to working with mathematical models. As the overall population-level HIV incidence declines, long-acting PrEP is no longer cost saving; however, it is still very cost-effective as compared to standard PrEP (incremental cost-effectiveness ratio, \$680 per year of life saved as the incidence halves from the base case). Interestingly, even longer use of long-acting PrEP (ie, past the age of 25 years) only incrementally increases costs but has impressive impact on reductions in the lifetime HIV risk, whereas shorter durations of use (eg, only to 19 years of age), while requiring less investment of capital, do not avert enough HIV infections to make that smaller investment cost-effective. This finding highlights the importance of a nuanced and thorough understanding of the acceptability and predictors of persistence to injectable PrEP required to optimize prevention benefits.

In a sobering analysis, the authors note that, to achieve 50% coverage of high-risk young women in South Africa, it would cost \$1.6 billion over 5 years. This signals the massive investment that would be required to deploy and scale-up injectable PrEP use, assuming that its safety and efficacy are demonstrated. This dollar

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amount is a clarion call to action for the marshaling of political will and global resources that need to be brought to bear on South Africa's epidemic. The data to support such rollout and scale-up are still 5–10 years away, providing a window of opportunity to prepare. Should both standard PrEP and long-acting PrEP be made generally available in South Africa, >50% coverage might be possible via the opportunity for greater biomedical product choice but at an intermediate overall cost between the CEPAC cost estimates for standard and long-acting PrEP.

Considering the advantages of long-acting PrEP with regard to the potential for improved adherence, there are also important new considerations and pitfalls. An important issue will be the impact of the potential failure of long-acting PrEP on the subsequent response to ART: the prolonged pharmacologic tail when long-acting PrEP is discontinued provides a prolonged window of potentially subprotective drug levels as the product decays or washes out over a period of up to 52 weeks after the final injection. HIV acquisition during the washout period could lead to selection of resistant viral quasispecies. In the case of TMC278LA (long-acting rilpivirine), resistance could compromise subsequent virologic responses to efavirenz-based first-line therapies, as has already been seen in a participant during early 278LA studies [13]. Whether and how individuals transitioning away long-acting PrEP should be covered by other prevention methods will add an extra layer of complexity and, potentially, cost to long-acting PrEP rollout.

The parity between standard and long-acting PrEP assumed in the analyses by Walensky et al is predicated on a comparable benign safety profile of all the agents being studied. It is important to remember that the extended pharmacokinetic exposure profile—so attractive for potentially providing durable protection after infrequent administration—also carries substantial risk in the event of toxicity. Neither agent in advanced phases of clinical development can be removed once

administered—the agents are not dialyzable, nor can the injected depot be surgically removed to minimize drug exposure. Toxicity management during an oral run-in phase with a short-acting oral formulation of the long-acting product is likely to be an obligate part of any long-acting strategy until there is a more-robust safety database available for the long-acting preparation, and will almost certainly be part of any Food and Drug Administration labeling should one of these products reach regulatory approval milestones. Optimizing adherence to the daily oral product during the oral lead-in period to ensure a level of exposure that is sufficient to establish (or rule out) toxicity is yet another level of added complexity but is a necessary part of testing a long-acting injectable drug.

Through the lens of women's health, successful long-acting injectable PrEP has the potential to have an impact beyond the consumer herself: childbearing years are likely to be accompanied by condomless intercourse, and pregnancy itself increases both the susceptibility to HIV infection and the seriousness of seroconversion, vis-à-vis the potential for vertical transmission in the context of extremely high levels of plasma viremia during acute infection. The potential to reduce or eliminate such transmission is not an easily modeled secondary benefit of successful PrEP. Moreover, although aspirational, the theoretical potential to combine an injectable contraceptive with long-acting injectable PrEP for deployment as a directly observed set of injections during a single healthcare visit is extremely tantalizing.

Walensky et al have provided a road map of financial requirements to accomplish implementation of both standard and long-acting injectable PrEP for South African females, as well as robust financial and epidemiologic justifications for these interventions. If long-acting PrEP proves to be safe and efficacious, it will be up to policy makers, financiers, treaters, and potential consumers to advocate that the map be followed.

Note

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