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The critical importance of retention in HIV prevention

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Pre-exposure prophylaxis (PrEP) has revolutionised the HIV prevention landscape; long-acting injectable formulations are in development, and are heralded as an alternative that removes the daily pill burden and associated adherence challenges of oral PrEP.[1] In *The Lancet HIV,* Brandon Marshall and colleagues[2] report the results of a modelling study that compared effectiveness of exclusive long-acting injectable PrEP implementation with that of exclusive oral PrEP implementation in a virtual population of men who have sex with men in Atlanta, GA, USA. The investigators simulated HIV transmission over 10 years, with scenarios of varying population coverage and sensitivity analyses by maximum efficacy, drug half-life, and rates of retention in preventive care. At every coverage level, long-acting injectable PrEP resulted in fewer cumulative HIV infections than did oral PrEP. This superior performance was attributable to two key assumptions: high efficacy of long-acting injectable PrEP and 12 months of waning partial protection after final injection.

This study, although thoughtfully researched and rigorously specified, draws attention to the strengths and limitations of modelling studies for informing implementation. The study's findings also emphasise what is soon to be the single most crucial issue in PrEP implementation, namely retention. First, consider why retention—and not adherence—is of primary importance. As the investigators specify in their model, data suggest that more than 92% of oral PrEP users are optimally adherent (ie, they take four or more pills per week).[3] Long-acting injectable PrEP might relieve a daily adherence burden for PrEP users, but should not be seen as a remedy for an adherence problem among users of oral PrEP, because there is no evidence that such a problem exists.

Why is retention so crucial? To amend the words of former Surgeon General C Everett Coop: drugs don't work if people don't have them. Daily non-adherence is not a problem for oral PrEP, but extended periods of non-adherence (ie, because patients have insurance lapses or have missed appointments necessary to refill prescriptions) present a major problem. In this model, retention of people on oral PrEP in clinical care was estimated at 59–6% after 6 months,[2] but anecdotal data from community-based clinics suggest that this percentage might be even higher.[4] A certain percentage of discontinuation could be intentional (ie, patients actively decide that they no longer want to take oral PrEP). However, a much larger

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percentage is probably caused by logistical or financial barriers to PrEP care. Insurance lapses and coverage gaps place an extraordinary burden on people using PrEP, and are most likely to negatively affect individuals who need PrEP most.[5] At present, daily oral PrEP guidelines require clinical visits every 3 months for refills; this level of investment raises an unnecessary hurdle for patients with inflexible schedules or high insurance payments. Quarterly testing and treatment of PrEP users for HIV and other sexually transmitted infections is a priority, but we must think creatively about solutions that reduce financial and logistical barriers to PrEP retention. If retention is the problem rather than adherence, then a more frequent (every 2 months) schedule of visits for long-acting injections might generate more problems than it resolves. Ironically, in Marshall and colleagues' model, low retention on long-acting injectable PrEP was a population-level benefit because discontinuation rates were offset by an influx of new users, resulting in higher numbers of individuals with waning partial coverage. On the one hand, these modelling data are of major importance because they might mitigate reluctance to prescribe long-acting injectable PrEP to individuals who could be deemed more likely to fall out of care. Implicit bias in HIV-related prescribing has been well documented and disproportionately affects individuals who might benefit most (eg, people who inject drugs, uninsured individuals, people of colour).[6,7] On the other hand, the model's assumption of a steady state of new users of long-acting injectable PrEP is unlikely in an implementation context because many of the social and financial barriers that drive loss to follow-up in PrEP care are the same barriers that negatively affect PrEP uptake in the first place.

We must also consider the role that the extended half-life of long-acting injectable PrEP might have in decision making by patients and providers. In conversations about daily oral PrEP, patients often have questions and concerns about their ability to discontinue the medication when it is no longer needed, or in the event of side-effects.[8] Concerns about the presence of a long-acting drug in the body and about resistance following a final injection might lead to reservations about long-acting injectable PrEP as an HIV prevention strategy. Similarly, provider concerns about how to talk to patients about the drug's half-life, and the ability of patients to understand the concept, might interact with implicit biases to affect willingness to recommend long-acting injectable PrEP to specific types of patients.

Modelling studies can provide important insights into the hypothetical potential of a novel intervention, but they are limited in their real-world application. At first glance, the superiority of long-acting injectable PrEP seems to be the result of its inherent properties (ie, efficacy and half-life). However, upon deeper inspection, the superior population-level efficacy of long-acting injectable PrEP will manifest only in the context of the real-world behaviour of patients, providers, and systems. Social and behavioural research is crucial to ensure that the necessary supports are in place to improve decision making, uptake, and most importantly, retention of new biomedical prevention products.

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