

## Moving HIV PrEP from research into practice



Pre-exposure prophylaxis (PrEP) for HIV has been studied in five large and rigorous randomised controlled trials, three of which showed efficacy,<sup>1-5</sup> but several questions remain. Is PrEP a useful public health intervention? Will those most at-risk use it? Will they adhere to it? What is its real-world safety profile? And will it reduce or increase high-risk sexual behaviour and HIV incidence?

In *The Lancet Infectious Diseases*, Robert Grant and colleagues<sup>6</sup> report the results of iPrEx Open-Label Extension, the first open-label study of PrEP. They enrolled 1603 HIV-negative men and transgender women who have sex with men who previously were participants of three randomised double-blind PrEP studies (iPrEx, ATN 082, and US Safety Study).<sup>7,8</sup> Follow-up lasted 72 weeks after enrolment.

Uptake of PrEP was high: 76% of participants opted to take PrEP at some point during follow-up. Those reporting condomless receptive anal intercourse and those who were herpes simplex virus 2 seropositive were more likely to start PrEP. Incidence among participants who did not use PrEP was 2.6 infections per 100 person-years versus 1.8 infections per 100 person-years for those who did use PrEP, with the difference being non-significant but perhaps clinically important: HIV incidence in the placebo group of the randomised iPrEX study was 3.9 infections per 100 person-years.

Adherence (as measured by drug concentrations in dried blood spots) was better among older participants, those with more education, and those who engaged in riskier sexual behaviours (according to several measures). No incident HIV infections occurred in participants with drug concentrations commensurate with taking four to seven tablets per week. Side-effects were few. Reports of condomless receptive anal intercourse fell over the course of the study—for both on-PrEP and off-PrEP participants. The most common pattern of use of PrEP was initial uptake with subsequent fall-off.

Is PrEP uptake by 76% of participants enough? Because the participants were in a previous trial, the sample is biased towards a highly motivated population; therefore one might have expected nearly universal uptake. Toxic effects do not seem to be limiting uptake: “participant preference” was the most common reason

for drug interruption. Are daily-dosing fatigue or the stigma of using a drug that has been saddled with an association with promiscuity contributing to attenuated adherence despite persistent or increased risk?

Optimisation of prevention combinations is crucial to overall success of efforts to eliminate HIV. The overall HIV incidence for those receiving PrEP in the open-label extension was 1.8 infections per 100 person-years, compared with the 2.2 per 100 person-years for those assigned to active tenofovir and emtricitabine in the parent-blinded iPrEX study. Why are incidences with open-label treatment not vanishingly low? iPrEX wisely combined drug prophylaxis with other HIV prevention services, but it seems that even this approach is insufficient.

The open-label extension study shows that four or more doses (on average), as assessed by dried blood spots, provided nearly complete protection against HIV acquisition. But how does the timing of missed doses—and particularly multiple missed doses—attenuate efficacy? It is inadvisable to interpret these findings in a way that encourages less-than-daily dosing at present.

Decreases in condomless receptive anal intercourse, reported in both on-PrEP and off-PrEP groups, supports the potency of the study’s prevention package and suggests an absence of much-feared risk compensation in an open-label study. It will be particularly important to see whether this finding holds true beyond clinical trial settings. The incidence of syphilis was much the same in on-PrEP and off-PrEP participants, although we do not have a full dataset for all incident sexually transmitted infections to fully interpret these findings.

Finally, only one case of treatment-emergent viral resistance (Met184Val) was reported. The study allowed at maximum intervals of 12 weeks between visits for HIV testing; therefore patients infected soon after a visit could spend almost 3 months taking non-suppressive tenofovir and emtricitabine, increasing the selection pressure for resistant viral species. How often resistance to emtricitabine develops, and whether seroconversion with tenofovir-resistant virus occurs will be important to see in clinical practice.

WHO and the US Centers for Disease Control and Prevention recommend the broad use of daily oral PrEP for HIV prevention in at-risk populations,<sup>9,10</sup>



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acknowledging the urgent need for new prevention strategies, and the need to provide clinicians with concrete guidance on the use of a complex and nuanced intervention. Although the study of Grant and colleagues advances our understanding of oral PrEP, and informs the thresholds of protection, it raises nearly as many questions as it answers. We eagerly await the upcoming results from a cadre of open-label studies in which tenofovir and emtricitabine is being provided to people who have not previously participated in pivotal randomised studies. Because choice between prevention options remains paramount to successful HIV prevention, we also look forward to the development of new drugs and preparations for PrEP, including topical gels, injectable antiviral drugs, and immunotherapies. The future is rich with possibility, but we have far to go to realise the full potential of PrEP.

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