Reassuring long-term safety, resistance, and efficacy data for two daily formulations of PrEP

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In *The Lancet HIV*, David A Wohl and colleagues[1] report the final open-label extension phase of the DISCOVER trial, providing reassuring evidence of the efficacy and safety of long-term use of oral emtricitabine and tenofovir alafenamide for pre-exposure prophylaxis (PrEP). In the open-label extension phase, participants who completed the 96-week randomised controlled phase of the study in the emtricitabine plus tenofovir disoproxil fumarate group were offered the opportunity to switch to emtricitabine plus tenofovir alafenamide; participants in both groups could then continue for a 48-week extension period. The number of new infections continued to be very low, adding only three new HIV acquisitions during the additional 48-week open-label use of emtricitabine plus tenofovir alafenamide to the 23 that happened over the previous 96-week study and one that happened between week 96 and the beginning of the open-label extension period. These data confirm low and similar rates throughout the trial in both the emtricitabine plus tenofovir disoproxil fumarate and emtricitabine plus tenofovir alafenamide groups.

This extended follow-up study also confirms the long-term relative safety profiles of these drugs. Emtricitabine plus tenofovir alafenamide shows a favourable kidney function profile. The small decreases in bone mineral density observed with emtricitabine plus tenofovir disoproxil fumarate use were reversed after switching.[1,2] Similarly, the well documented bodyweight and lipid suppressive effects of emtricitabine plus tenofovir disoproxil fumarate were confirmed, with reversal of these effects after switching. This additional open-label extension phase adds to our understanding of the trade-offs of these PrEP regimens and will help guide patient choices, along with considerations of access and cost.

New to this analysis of the DISCOVER study is an evaluation of the potential for RNA testing to find infections earlier, which could reduce the risk of developing resistant virus after infection. For both concerns, the DISCOVER data are very reassuring regarding daily oral prevention drugs. By analysing samples collected during previous study visits, early HIV detection through RNA testing found only four of 23 incident cases with available samples. Delay in the detection of HIV with rapid testing is known to occur for a small proportion of people due to a delay in the development of antibody response. Therefore, this number of participants with delayed detection of infection falls within what might be expected due to natural variation in HIV infection. A small proportion of infections could be detected earlier through RNA testing, but sustained delays in detection of infection, even with daily use of oral drugs for HIV infection, are rare.[3] As determined by Wohl and colleagues, RNA testing does not add substantial benefits to management of HIV PrEP while adding substantial cost and complexity. Therefore, I support the pragmatic approach recommended per WHO guidance,[4] in which RNA testing is not part of routine PrEP monitoring. Additionally, no resistance was detected among the incident cases. This finding aligns with previous PrEP trials on oral emtricitabine plus tenofovir disoproxil fumarate in which resistance in incident infections was rare.[5]

In the context of long-acting injectable antiretrovirals, current evidence on the risk of resistance is slightly different. In a randomised trial comparing injectable cabotegravir with oral emtricitabine plus tenofovir disoproxil fumarate in cisgender men and transgender women who have sex with men,[6] continuous exposure to cabotegravir after breakthrough infection resulted in the development of resistance in four of nine participants. However, with continuous exposure to cabotegravir, there was a two-thirds reduction in the risk of HIV acquisition compared with oral emtricitabine plus tenofovir disoproxil fumarate (0·41 per 100 person-years *vs* 1·22 per 100 person-years).[6] Overall, long-acting PrEP is a powerful tool to prevent HIV acquisition.

Although concerns around risk of development of resistance if infection occurs while on oral PrEP are valid, in the presence of these drugs, 90% of infections are averted,[7] and hence there are profound benefits in the simple and pragmatic implementation of PrEP for the prevention of HIV.

I declare no competing interests

Deborah Donnell
deborah@fredhutch.org

Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle, WA 98109, USA

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Low-cost point-of-care urine test to enhance PrEP adherence

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Tenofovir disoproxil fumarate combined with emtricitabine, used as pre-exposure prophylaxis (PrEP), has proven to be highly effective in preventing HIV among individuals at high risk of infection,[1] such as men who have sex with men[2] and serodifferent couples.[3] Efficacy is directly related with the number of doses, increasing from 76% when taken 2 days per week to 99% when taken daily.[4] As depicted, the success of a PrEP programme depends on adherence, which requires an efficient monitoring system to promptly identify individuals with suboptimal adherence.

Subjective measures of adherence, such as self-report and pill count, have the advantages of being inexpensive and easy to implement. However, they have substantial limitations in terms of accuracy and reliability.[5] Owing to these limitations, PrEP adherence has been assessed by use of pharmacological drug concentration assays (tenofovir or tenofovir disoproxil fumarate) in various biomatrices such as plasma, hair, and dried blood spot.[6]

In most pharmacological assays, therapeutic drug monitoring is carried out by use of liquid chromatography–tandem mass spectrometry, considered the gold-standard technique owing to its unmatched accuracy and precision. However, despite its superior analytical performance, liquid chromatography–tandem mass spectrometry comes with substantial costs—not only for the assays themselves but also because of the expensive equipment, the need for specialised professionals, and the time required to obtain results.[7] These factors pose barriers to its widespread use in health services, particularly in expanding PrEP programmes in low-income and middle-income countries. Consequently, there is a pressing need for more cost-effective alternative assays to facilitate broader access and implementation.

It is within this context that the study reported in this issue of *The Lancet HIV* by Monica Gandhi and colleagues is set.[8] The authors used a low-cost point-of-care immunoassay, similar to the test used for COVID-19, to detect short-term adherence on the basis of the concentration of tenofovir disoproxil fumarate in urine. A positive outcome indicated that a participant had taken a dose of the medication within the past 4 days. Considering the test provides results within 3 min, the authors aimed to measure the effect that immediate feedback from health-care professionals, based on the test results, can have on improving medication adherence among participants.

To accomplish this objective, they carried out a randomised study with two arms involving Kenyan women without serodifferent partners, the group at higher risk of HIV exposure in sub-Saharan Africa.[9] The women were enrolled at their 3-month routine visit after PrEP initiation and were followed quarterly for 12 months. All participants received PrEP and underwent urine testing at each visit. However, only one group received feedback based on the test results, whereas the other group received standard adherence support, as the health-care providers were unaware of the test results.

The effect of test-informed feedback was assessed by comparing the proportion of adherent women in the two groups. As the effect of the test-informed feedback might not be restricted to short-term adherence, Gandhi and colleagues[8] used information on hair tenofovir