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Person-centered HIV PrEP for cisgender women

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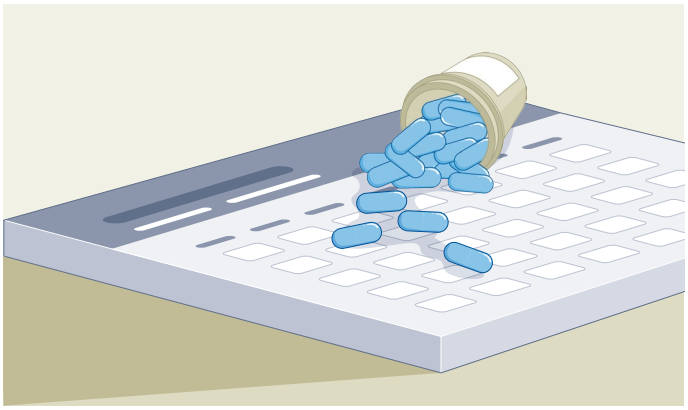
Two modelling studies offer compelling evidence that less-than-perfect adherence to HIV pre-exposure prophylaxis can still provide reasonable protection for cisgender women — providing optimism for a more person-centered approach and lower discontinuation rates.



Despite 1.6 million people taking at least one dose of safe, effective and affordable antiretroviral-based HIV pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate and emtricitabine (TDF/FTC), there were 1.3 million new HIV infections in 2022, most in cisgender women[1]. A major challenge for this (often young) population group is maintaining 100% daily adherence to oral PrEP[2,3].

Whereas the relationship between the number of pills taken per week and PrEP efficacy has been well-defined in cisgender men who have sex with men (MSM)[4,5], there is limited understanding of the relationship between adherence and efficacy in cisgender women — with a paucity of data from placebo-controlled clinical trials. This uncertainly is a barrier to person-centred counselling around adherence and timing of doses for women, who may themselves be aligning adherence to periods of risk[6]. Two papers in this issue of *Nature Medicine*[7,8] have brought together pharmacokinetic studies and data from multiple trials to model the adherence–efficacy relationship for TDF/FTC in cisgender women — or, put simply, to answer the question of how many pills a week is enough?

Moore et al.[7] analysed results from three placebo-controlled trials, which had data on short-term PrEP adherence (inferred from plasma levels of tenofavir (TVF)) and HIV incidence, and imputed longer-term adherence using data from HPTN082, a trial that measured levels of both TVF and TFV-diphosphate (a marker with a longer half-life) — enabling correlations between short (up to 3 days) and longer-term (1–2 months) adherence to be estimated. Their results suggest that those who took an estimated 2, 4 or 7 pills per week had 59%, 84% and 96% lower HIV incidence, respectively[7]. Although the confidence intervals are wide, these data suggest a dose–response relationship between adherence and protection among cisgender women. In a separate study, Zhang et al.[8] also modelled the adherence–protection relationship for PrEP in cisgender women and explored whether systemic or genital-tract levels of drug correlate better with HIV protection. They show that with three doses per week, median efficacy is 95% (confidence interval: 90–98%), but efficacy drops substantially at one dose per week. Their simulations show that if drug concentration in exposed tissue is added to the model (for example, vaginal tissue in the context of receptive vaginal intercourse), the predicted efficacy in fully adherent women would be substantially lower than the actual efficacy shown in clinical studies. From this inconsistency, they infer that longer-term adherence (represented by TFV-diphosphate) is a better correlate of HIV protection than drug concentration in the genital tract[8]. These studies suggest a similar adherence–efficacy relationship to that seen in MSM, and together, these data reassure us that 4–6 pills per week, although less effective than 100% daily adherence, provides levels of protection from HIV acquisition that fall somewhere between 85% and 95%[7,8]. Of note, the lowest level of confidence (52% efficacy) predicted by these studies for at least 4 pills per week is similar to the assumed vaccine efficacy incorporated into cost-effectiveness models of potential HIV vaccines[9].

A recent observational meta-analysis of 11 demonstration projects of TDF/FTC in cisgender women ($n = 6{,}296$) defined four types of adherence — consistently daily; consistently high; high but declining; and consistently low. In the 100% daily adherent group, there were no seroconversions, and in the 'consistently high' group (4–6 tablets per week), HIV incidence was 0.13%[10]. Data from MSM collected during studies of event-driven PrEP show no HIV acquisition in those who took 4–7 tablets per week[4,5]. These data in men and women are consistent with the findings from Moore at al.[7] and Zhang et al.[8]. However, for studies in MSM, we know that the 4 tablets taken for event-driven PrEP is concentrated around condom-less sex, but for trials or observational cohorts of cisgender women, we do not know the timing of PrEP use in relation to condom-less receptive vaginal intercourse. This makes any inference around timing of the PrEP dosing for women a challenge.

Effective long-acting PrEP — such as injectable cabotegravir taken every two months — is being introduced and may address some of the adherence issues seen with daily oral PrEP. However, it will be more expensive and requires healthcare worker administration and monitoring. TDF/FTC is cheaper, widely available, safe in pregnancy and requires only regular HIV testing, conducted by lay healthcare workers or through HIV self-tests[11]. These characteristics make it easy to integrate TDF/FTC within sexual and reproductive health and antenatal services, or to decentralise care to community-based lay healthcare

workers, peer outreach workers, and pharmacies[3,11]. Decentralization and integration have led to wider access, with nearly 5 million PrEP initiations by Q2 2023, according to the global PrEP tracker.

The Achilles' heel of TDF/FTC in cisgender women has been the emphasis on 100% daily tablet-taking, which can prevent young women from initiating treatment and, importantly, drives high PrEP discontinuation rates[2]. A frequently cited reason for stopping is 'Why take a pill a day to stop taking a pill a day?' – a reference to the similarity between daily TDF/FTC and daily antiretroviral therapy, and the insistence in both settings on 100% adherence. The papers by Moore et al.[7] and Zhang et al.[8] suggest that there is scope for more person-centred advice around 'good enough' adherence for those women who can take 4–7 tablets per week. Instead of the current emphasis on only 100% daily adherence, we can encourage daily pill taking but focus counselling on drug continuation; indeed, fewer than half of all women starting PrEP in Africa currently collect their second prescription. This will enable a range of PrEP options and delivery models for women.

Although the studies from Moore et al.[7] and Zhang et al.[8] rely on simulations, they both reached similar inferences that replicate observational data from entirely different studies. Both studies are limited by the fact that the models assume a uniform level of HIV acquisition risk alongside the adherence data, while evidence is emerging that adherence may change in line with different levels of HIV risk[6]. Because we do not know the timing of pill taking in relation to condom-less sex, it is not possible to confidently recommend event-driven PrEP among cisgender women based on these analyses. Finally, these studies have not explored the effect of less than 100% adherence on acquiring HIV drug resistance, although this may be offset by overall reductions in HIV incidence[12].

In conclusion, although we have entered an era in which we have a range of antiretroviral therapy-based prevention options for cisgender women, including long-acting injectable and vaginal rings, evidence in these studies reassures us that for those women who are able to persist in taking between 4–7 tablets per week, TDF/FTC is an effective, accessible and affordable choice of PrEP regimen.

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Competing interests

The authors declare no conflict of interest.