Title: Where next with PrEP?

Authors:

Diarmuid Nugent
UCL Centre for Sexual Health and HIV Research
The Mortimer Market Centre
London WC1E 6JB

Richard Gilson*
UCL Centre for Sexual Health and HIV Research
The Mortimer Market Centre
London WC1E 6JB

*Corresponding author

Acknowledgements

None

Financial support and sponsorship

None

Conflicts of interest

None

Abstract

Purpose of review

Controlling the HIV epidemic remains a major public health challenge and there is an urgent need for novel prevention strategies. Pre-exposure prophylaxis (PrEP) refers to the use of antiretrovirals in HIV-negative people at high risk to prevent infection and has the potential to be an important component in the global effort to end the HIV epidemic by 2030. We review the current evidence for the safety and efficacy of PrEP in its different forms and address emergent issues and concerns regarding its implementation.

Recent findings

Two further randomized control trials report high efficacy of both daily and intermittent PrEP in men who have sex with men (MSM) leading to renewed calls for wider availability of PrEP for this group. Oral tenofovir disoproxil/emtricitabine has been licensed for PrEP in many countries and is well tolerated, safe and effective.

Summary

Oral PrEP is safe and effective in reducing the incidence of HIV infection in individuals at high risk. Implementation in high income countries is progressing slowly; demonstration projects and trials continue in low and middle income countries.

Keywords: HIV prevention, PrEP, Pre-exposure prophylaxis

Key Points

- Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medication by people who are HIV-negative to prevent them from acquiring HIV
- Most PrEP trials have used containing a fixed dose combination of tenofovir and emtricitabine
- Tenofovir-based PrEP is highly effective in preventing HIV infection in those who take it regularly
- PrEP implementation is beginning but proceeding slowly in many countries amid fears about cost, long-term effectiveness and negative impacts on other STI rates, despite

economic analyses which have shown it to be highly cost effective, but sensitive to the price of the drug.

Introduction

Controlling the global epidemic of HIV remains a major public health challenge. HIV incidence in some adult populations has been static since 2010, challenging efforts to end the epidemic by 2030[1]. Indeed, rates have increased in some regions and certain at-risk groups [2, 3] highlighting the urgent need for new prevention strategies. Traditional approaches to HIV prevention have focused on behavioural change including encouraging the use of male condoms and negotiating safer sex, linked to regular HIV testing.

Biomedical interventions with proven efficacy in reducing HIV transmission include male circumcision [4, 5] and the use of early antiretroviral therapy (ART) to reduce infectivity, so called treatment as prevention (TasP). As a strategy, this relies on a high proportion of infected individuals being tested, linked to care and starting ART. Post-exposure prophylaxis (PEP) refers to short course ART to reduce the risk of HIV acquisition following a potential occupational or sexual exposure [6]. Despite the absence of robust randomized control trial (RCT) evidence it is widely available, and used, by some groups such as men who have sex with men (MSM) in high income countries. Yet the incidence in many diverse populations in high and low-income countries remains high, so new approaches to prevention are still needed.

Pre-exposure prophylaxis (PrEP) refers to the use of antiretroviral medication by people who are HIV-negative, in advance of a potential exposure, to prevent them from acquiring HIV [7]. There is now strong evidence that PrEP is safe and effective in preventing HIV infection and it is recommended for individuals at substantial risk in a number of countries [8**,9,10,11]. However, implementation is proceeding slowly amid fears about cost, long-term effectiveness and negative impacts on other STI rates.

Evidence for the effectiveness of PrEP

Most PrEP trials to date have used oral tenofovir disoproxil fumarate (TDF), a nucleotide reverse transcriptase inhibitor (NRTI) used for the treatment of HIV and

chronic hepatitis B. It is available as a fixed dose combination with another NRTI, emtricitabine (FTC), marketed as Truvada®. Pre-clinical studies established the efficacy of PrEP in animal models. Oral TDF-FTC prevented infection after vaginal inoculation with HIV-1, in humanized mice [12}. Trials in macaques also found a protective effect of tenofovir against simian HIV (SHIV) infection following rectal or oral exposure [13, 14, 15].

Ten RCTs evaluating PrEP in humans have been published since 2010 of which 8 included oral TDF or TDF-FTC. In the iPREX study, 2499 men or trans-gender women who have sex with men, were assigned to receive daily TDF-FTC or placebo. 36 new HIV infections were detected in the treatment group compared to 64 in the placebo, an efficacy of 44% [16]. Partners PrEP enrolled 4758 serodifferent heterosexual couples in Kenya and Uganda where the HIV-positive partner was not on ART. HIV-negative partners were assigned to receive either TDF-FTC, TDF alone or placebo. There was a 67% reduction in HIV incidence in the TDF group and 75% in the TDF-FTC group, relative to placebo; in those with detectable TDF in plasma there was an 86% reduction [17]. The TDF2 study recruited 1219 sexually active HIV-negative men and women in Botswana; daily TDF-FTC PrEP was associated with a reduction of 62.2% in HIV acquisition relative to placebo in the modified intention-to-treat analysis [18]. The Bangkok TDF study enrolled 2413 injecting drug users randomized to either TDF alone or placebo. 33 people acquired HIV in the placebo arm compared to 17 in the TDF arm, a reduction of 48.9% [19]. All these studies showed that adherence to the PrEP regimen, as evidenced by detectable TDF in plasma, was closely correlated with efficacy.

Two large RCTs failed to demonstrate a protective effect of oral TDF-based PrEP. FEM-PrEP assigned 2120 HIV-negative women in Kenya, South Africa and Tanzania to either oral TDF-FTC or placebo. HIV infections occurred in 33 women in the TDF-FTC group and in 35 women in the placebo group [20]. VOICE enrolled 5029 women in South Africa and participants were assigned equally to TDF alone, TDF-FTC, or placebo. There were 52 HIV seroconversions in those receiving oral TDF, 61 in those receiving TDF-FTC and 60 in those receiving placebo with no significant difference between the treatment group and placebo [21]. In both studies, however, the estimated adherence to the study drugs was low; in FEM-PrEP less than 40% of participants had evidence of

recent pill use based on plasma tenofovir levels, and in VOICE 58% and 50% of women in the TDF and TDF-FTC arms respectively had no detectable plasma tenofovir on any quarterly plasma sample. Modelling data from the open label extension of the iPREX study suggests that daily TDF-FTC PrEP achieves plasma drug levels greatly in excess of the protective threshold and that 2-3 tablets per week may be sufficient [22]. However this data is from a cohort in whom anal intercourse is the main risk factor for HIV and evidence is lacking on the level of adherence required to protect against vaginal exposure.

Recent reports from two RCTs in MSM have added important new evidence to guide policy on PrEP. The PROUD trial [23*] addressed the question of whether risk compensation, whereby individuals may engage in riskier sexual behaviours when they perceive themselves to be protected by PrEP, would negate the efficacy demonstrated in double-blind RCTs [24,25]. The trial recruited MSM reporting condomless anal intercourse (CLAI) within the previous 90 days, and likely to do so again in the next 90 days. Participants were randomized to receive oral TDF-FTC PrEP immediately, or defer PrEP for 1 year. Importantly, the trial was open label so as to capture the net effect of efficacy, adherence and any change in sexual behaviour and hence provide insights into how effective PrEP might be in routine use. The enrolment of 544 participants was intended as a pilot but an unexpectedly high incidence of HIV infection in the deferred group prompted the steering committee to advise PrEP be offered to all in the deferred group immediately. HIV infection occurred in 3 participants in the immediate group versus 20 in the deferred group, a relative reduction of 86%. Continued follow-up was undertaken to gain more evidence on longer-term use.

Evidence from macaque studies had shown intermittent PrEP dosing around the time of exposure to be at least as effective as daily prophylaxis [13, 26]. The IPERGAY study [27*] examined the efficacy of "event-related" PrEP in MSM reporting CLAI with 2 or more partners in the last 6 months. 400 participants were randomized to receive oral TDF-FTC or placebo and were instructed to take 2 tablets 2-24 hours before intercourse followed by 1 tablet 24 and 48 hours later, or a daily pill until 2 days after the most recent exposure in the event of multiple episodes of intercourse. There were two new HIV infections in the TDF-TFC group versus 14 in those taking placebo representing an

86% relative reduction, identical to the effect observed in PROUD. Of the two participants in the treatment group who acquired HIV, neither had detectable plasma drug levels and each returned most of their pills so were clearly non-adherent.

A recent systematic review of PrEP trials [28**] noted the correlation between effectiveness and proportion with detectable drug levels. The two studies which failed to find an effect of PrEP were both in women participants leading to speculation that lower concentrations of TDF in vaginal versus rectal tissue may contribute to the lower efficacy, as well as suggesting that regular dosing may be more important in women [20,29]. The reasons for poor adherence in VOICE and FEM-PrEP are likely complex and multi-factorial. In FEM-PrEP the majority of participants perceived themselves to be at low or no risk of HIV [20]. A placebo-controlled trial design may reduce adherence, given that the participant knows it may be a placebo [23, 25]. Event-related PrEP may offer potential advantages in reduced pill burden, cost and potential drug toxicity. However, efficacy has been demonstrated in only one trial in MSM and cannot necessarily be applied to other risk groups. Moreover participants in IPERGAY took a median of 15 pills per month and the authors emphasise that their results cannot be extrapolated to those with less frequent exposure taking a more intermittent regimen [27]. Although animal models have suggested that TDF-FTC may be more effective than TDF alone [13] a recent trial in a heterosexual population showed no difference [30]; further evidence is needed for MSM populations.

Alternatives to oral TDF-containing PrEP

Three RCTs have evaluated the effectiveness of a vaginal gel formulation of tenofovir used pericoitally (CAPRISA, FACTS 001) or daily (VOICE). CAPRISA demonstrated a modest reduction in HIV incidence of 39% in the active treatment arm in a trial of 889 women randomised to receive either tenofovir 1% gel or placebo. This increased to 54% in a subset of high adherers [31]. Both VOICE [21] and FACTS 001 [32] failed to demonstrate efficacy. Adherence was low in both trials, although a subset analysis in women with detectable drug levels did suggest it had efficacy.

Longer-acting modes of drug delivery offer the potential to overcome the adherence issues observed with PrEP requiring daily or coital use. Two studies have reported on a sustained release vaginal ring (to be changed monthly) containing dapivirine, a non-nucleoside reverse transcriptase inhibitor. MTM-020-ASPIRE [33] demonstrated a 27% reduction in HIV acquisition and IMP-027 [34] a 30.7% reduction relative to placebo. Again, sub-group analyses demonstrated greater efficacy in those with objective evidence of adherence. Phase 1 data for a tenofovir vaginal ring has recently been published [35]. It is important to note that vaginal delivery would give no protection for receptive anal intercourse. In the PARTNER study which examined HIV transmission between serodifferent couples, 23.8% of HIV-negative heterosexual women reported anal sex with their HIV-positive partner [36*].

Other agents for PrEP are being studied. Tenofovir alafenamide (TAF) is another prodrug of tenofovir with reduced potential for renal toxicity [37], also coformulated with FTC, and protective against rectal SHIV in macaques [38]. Clinical trials are underway to determine equivalent efficacy to TDF, with fewer restrictions and less renal monitoring. Maraviroc is an entry inhibitor for which safety and tolerability as PrEP have been demonstrated in Phase 2 trials [39]. Long-acting injectable antiretrovirals offer the possibility of monthly or even 2 monthly injections and Phase 2b/3 studies are planned [40,41].

Safety of oral TDF-containing PrEP

TDF and TDF-FTC have been used for the long-term treatment of HIV for almost two decades and are safe and well tolerated. Rates of adverse events in controlled PrEP trials were similar in active and controls [28**].

TDF may cause proximal renal tubulopathy in a small proportion of patients [42]. Small sub-clinical reductions in renal function were noted in i-PREX and the Bangkok-TDF study which were reversible on stopping PrEP. [43, 44]. However most studies excluded patients with a creatinine clearance of <50mls/min therefore PrEP cannot be considered safe in those with pre-existing renal disease and impaired creatinine clearance.

Several trials demonstrated small decreases in bone mineral density (BMD) during the first 24 weeks of PrEP use which did not progress thereafter. The risk of small BMD changes should be set against the benefit of PrEP in averting HIV infection with the need for lifelong ART.

Treatment of HIV infection with single or dual agent NRTI therapy is associated with the rapid development of viral resistance. There is therefore a risk of resistance if PrEP is commenced when there is undiagnosed HIV infection. It is essential to test for HIV prior to starting PrEP, and to be aware that some point of care antibody tests can remain negative for up to three months in acute HIV infection [45]. Repeat testing is therefore important soon after starting, and thereafter regular testing every 3 months, particularly in those who use PrEP intermittently.

In trials, the risk of resistance was low but greater in those treated with active PrEP versus placebo. In a systematic review and meta-analysis of six trials reporting resistance data, of 44 participants subsequently found to have had HIV at enrolment, 8 had TDF or FTC mutations of whom 6 had received active PrEP. Just 6 of 533 participants who acquired HIV post randomisation had TDF or FTC resistance of whom 5 were randomised to active treatment [28**]. Two of three PROUD participants with HIV infection at enrolment or at their 4 week visit had the reverse transcriptase mutation M184V, probably selected through exposure to FTC [23]. In the absence of a reactive point of care antibody test or clinical suspicion of acute HIV infection, in individuals with on-going high risk of HIV infection it is nonetheless preferable to start PrEP promptly rather than to delay it over theoretical concerns about resistance [8**]. With larger scale implementation of PrEP, active surveillance for changes in resistance patterns will be essential.

There is no known association between either TDF or TDF-FTC and adverse fetal or neonatal outcomes [42, 46]. Pregnant women are usually excluded from PrEP trials but may be at high risk of HIV infection and should therefore be considered for PrEP when clinically indicated.

Oral TDF and TDF-FTC are active against chronic hepatitis B infection, and there are concerns about the danger of hepatitis flares or liver injury if PrEP is discontinued [47]. Chronic hepatitis B was an exclusion criterion in most PrEP trials therefore data are limited. iPREX reported on 6 participants chronically infected with hepatitis B who received active PrEP; 5/6 had liver function tests 12 weeks after stopping treatment of whom one had a grade 1 elevation in transaminases [48]. Current guidance is to screen for active HBV infection in those starting PrEP [8**, 9, 10]. Daily PrEP is preferred over intermittent use.

Although a systematic review found no evidence that PrEP led to changes in sexual behaviour [28**] these findings may not apply to those taking PrEP outside of a research setting. The open-label nature of the PROUD trial, comparing PrEP with no PrEP, may provide a more realistic picture. Whilst there was no significant difference in self-reported sexual behaviour, bacterial STIs were numerically more common in the immediate PrEP group although the difference was not statistically significant [23*]. Further data is likely to emerge from open-label extensions of other studies and PrEP implementation studies.

The future of PrEP: looking towards implementation

Analyses covering varied settings and populations suggest that PrEP is cost-effective when set against the cost of long-term treatment and care for HIV [49, 50, 51]. However implementation in many countries is progressing slowly. Meanwhile some individuals are buying generic TDF-FTC, often from on-line suppliers. The quality and safety of drugs purchased in this way cannot be guaranteed, but voluntary groups and health services are helping to support patients with monitoring, and testing drug levels, to verify that the medication at least contains active drug. With limited programmes in place we are far from having equity of access.

The cost effectiveness of PrEP increases with the risk of HIV infection in the population, therefore targeting treatment to those at highest risk is important. Risk will also vary over time; when risk falls the need for PrEP may cease. Reports from PrEP trials show that those who withdraw or are lost to follow-up may be at risk. Whilst trials do not

suggest that PrEP modifies sexual behaviour to the extent that the benefits are lost, it is essential that those taking PrEP have regular HIV and other STI testing. Wider availability of PrEP may also result in uptake amongst those at lower risk, and continued surveillance of trends in STI rates and sexual behaviour will be important. The high rates of STI and substance use in PrEP users reported recently [52] emphasize that PrEP should be part of a broader package of sexual health care and harm reduction. Yet the overwhelming evidence for the efficacy, safety, tolerability and acceptability of PrEP means that it should be included as a key component in the global effort to control HIV infection in those populations at greatest risk.

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