Oral PrEP for HIV prevention. It works

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Abstract

There is an ongoing need for effective methods for prevention of HIV infection. A wide range of tools is needed, in varying social and economic contexts, and against different modes of transmission. Recent advances have concentrated on biomedical approaches to prevention, including the use of antiretroviral therapy (ART) prior to possible exposure to HIV: pre-exposure prophylaxis (PrEP).

Keywords: Pre-exposure prophylaxis, PrEP, iPERGAY, PROUD

Introduction

Almost 35 years since the first published reports of AIDS, the HIV epidemic continues; globally 2.1 million new infections occurred in 2013 [1]. The epidemic remains a significant challenge and prevalence amongst men who have sex with men (MSM) continues to increase in many countries [2,3]. There is an ongoing need for effective methods of prevention. A wide range of tools is needed in varying social and economic contexts, and against different modes of transmission. Recent advances have concentrated on biomedical approaches to prevention, including the use of antiretroviral therapy (ART) prior to possible exposure to HIV: pre-exposure prophylaxis (PrEP).

Drug prophylaxis is already frequently and successfully used in a variety of other settings, including the prevention of malaria and the oral contraceptive pill. Both oral and topical (to vagina or rectum) PrEP have been tested. In studies of oral PrEP, tenofovir (TDF) and tenofovir–emtricitabine (TDF-FTC) have been investigated. In this review we focus only on oral PrEP, for which more data are available, and for which the drugs that have been studied are currently available.

Evidence

The results of 10 randomised controlled trials (RCTs) of oral PrEP are available; they are summarised in Table 1. All studies investigated daily oral PrEP, with the exception of iPERGAY, which investigated 'on demand' PrEP timed around the period of exposure [4]. Of note, all studies combined PrEP with safer sex counselling and STI testing, highlighting the importance of PrEP within a package of holistic care.

The populations investigated include MSM and transgender women (TGW) [4–7], heterosexual men and women [8,9], heterosexual women only [10–12] and people who inject drugs (PWID) [13].

The overall estimate for the efficacy of oral PrEP in these studies ranges widely from -49% to 86% [5,12]. The discrepancy in results is almost certainly explained by adherence. In the two studies that were stopped early due to futility, drug was detected in less than 40% of participants [11,12]. However, adherence was also imperfect in studies that showed high efficacy (PROUD) [5]. PROUD showed an 86% reduction in HIV transmission in the intervention group, despite the fact that only 56% of intervention participants had enough drugs prescribed for full adherence [5]. More work is needed to establish the necessary frequency and

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dosing in order to gain optimal levels of protection. In addition, participant gender may contribute to discrepant overall results as TDF concentrates less well in vaginal tissue compared to rectal tissue [14]. This may mean that the required level of adherence to achieve efficacy may be higher for women.

Organisational responses

The US Food and Drug Administration (FDA) became the first national body to approve oral PrEP in 2012, which was subsequently followed by Centre for Disease Control (CDC) guidelines in 2014 [15,16]. The guidelines specified that PrEP should be twinned with a risk-reduction strategy to encourage use in combination with safer sex practices [15]. PrEP was approved for people at 'substantial risk' of HIV, including negative partners of any gender in serodiscordant relationships, high-risk MSM and PWID [16]. There is a relatively low threshold for the classification of 'substantial risk' and reasons include recent STI, high number of partners and inconsistent condom use.

Uptake of PrEP in the US has been slower than anticipated, possibly due to cost barriers and limited awareness amongst patients [17]. Analysis of pharmacy data indicates that around 3,000 people were prescribed PrEP in the first 2 years post–approval [18]. Initially over 40% of patients receiving PrEP were women [18], but more recent data indicate the proportion of men is increasing [19].

In the light of new data, the World Health Organization (WHO) lifted their initial requirement that PrEP was prescribed within a demonstration project [20]. In 2014, PrEP was included alongside other prevention tools such as condoms and peer–based education programmes in the WHO consolidated guidelines [21].

Outside the US, prescribing PrEP is more complicated, since no other countries have licensed the use of ART as PrEP. However, lack of a licence has not prevented the widespread use of ART as post-exposure prophylaxis (PEP), for which there is no randomised controlled trial data or indicated licence in many countries including the UK.

Despite evidence on the efficacy of PrEP, organisational responses have been notably cautious. The European Centre for Disease Control (ECDC), the British HIV Association (BHIVA) and the British Association of Sexual Health and HIV (BASHH) all issued public statements between 2012 and 2014 which acknowledged efficacy, but did not recommend widespread use at that point [22,23]. This was due to a number of concerns including adherence, behaviour change and cost. Following continuing publications showing strong evidence of efficacy, the potential use of PrEP is currently under review in many countries

and recommendations may change in the near future.

Issues

STIs/behaviour

Evidence as to whether PrEP will increase risk-taking behaviour and sexually transmitted infection (STI) incidence is mixed. Some studies have shown no evidence of increased risk-taking behaviour, such as a greater number of partners and condomless sex [6,8,11]. However, these results came from studies where participants were blinded as to whether they were taking active drug, and at a time when efficacy of PrEP was unknown.

Conversely, PARTNERS PrEP showed that when participants were unblinded, there was an increase in the frequency of sex with non-primary partners, although no increase in the frequency of condomless sex and no significant difference in diagnosis of STIs was observed [9]. In the open-labelled extension of iPREX, frequency of condomless sex and number of sexual partners was the same in groups receiving and not receiving PrEP [24].

PROUD aimed to understand PrEP use in a real-world setting in which participants knew when they were taking an active drug. Results showed that there was no significant difference between the immediate and deferred groups in terms of STI diagnoses, and reported sexual behaviour [5].

It is important to remember that PrEP only protects against HIV. These results show that although the use of PrEP does not necessarily lead to an increased risk, the act of seeking PrEP reflects that the patient identifies themselves as at high risk for HIV infection and, therefore, other STIs. The risk of other STIs may be less substantial where PrEP is used in the context of a monogamous relationship by serodiscordant partners. This highlights the importance of using PrEP in combination with regular STI screens, in addition to HIV testing and other HIV prevention strategies. If PrEP were to be rolled out without being part of a broader HIV prevention package, this could have a detrimental impact on risk behaviour and STI incidence. Any services that introduce PrEP will also need to ensure that PrEP is accessible to groups under–represented in PrEP clinical trials, in particular black and minority ethnic groups and TGW.

Resistance

Potential resistance has been repeatedly cited as a key concern around PrEP (Table 1). For participants taking PrEP, we calculate that resistance occurred in 4% (9/221) of cases where HIV was transmitted after enrolment. Resistance was observed in 3% (2/75) of participants in the intervention arm of TDF–only groups, compared to 5% (7/146) of those in TDF-FTC groups.

Resistance was particularly notable in participants undergoing seroconversion at the time of enrolment. In the TDF-FTC groups, 20 newly diagnosed cases of HIV were identified as having primary HIV at enrolment, among which resistance was observed in 9 (45%). In the TDF-only groups 20% (2/10) of participants with primary HIV at enrolment had resistant virus. A logical response might be to exclude anyone at risk of seroconversion from taking PrEP; however, since recent condomless sex is a key indication for PrEP, this approach is not practical and would exclude those who may benefit the most. An alternative may be to alert patients of this possibility beforehand and to advise them to seek medical advice immediately should they feel unwell in the weeks following PrEP initiation.

The impact of a single genotype resistance in high-income countries is minimal as there is a wide range of ART available. However, such resistance could be highly problematic in low- and middle-income countries where the available drug regimens are limited. When PrEP is used in a real-world setting, with less frequent testing and potentially poorer adherence, further resistance may be seen. It is vital that as countries license PrEP, they also initiate effective resistance surveillance systems to monitor resistance trends and inform future practice.

Side effects/toxicity

In both the TDF and TDF-FTC groups, the most commonly reported adverse events were gastrointestinal symptoms: nausea, vomiting, diarrhoea and abdominal pain [6,8]. Changes in renal function were also observed in some studies, but they tended to be mild and occurred in few cases [12,13]. Significant differences in renal function between intervention and control groups were only observed in the FEM PrEP and VOICE studies [11,12].

In keeping with their use as HIV treatment, both TDF and TDF–FTC appear safe for use as PrEP, although long-term data are lacking. Conversely, the low adherence seen in some studies may lead to an underestimation of the true prevalence of adverse effects. Full assessment of side effects and toxicity remains incomplete and long-term follow-up data are needed.

Cost-effectiveness

In the context of ageing populations and limited resources, health systems are under significant financial pressure. As a result, the potential cost of PrEP as an HIV prevention strategy remains a controversial issue.

Despite the cost, PrEP has the potential to be a cost-effective addition to existing HIV prevention strategies when used in the right setting, and targeted at high-risk populations [25]. It is also important to note that PrEP is unlikely to be taken life-long; instead it may be accessed during seasons of risk, including use of PrEP as a bridge to ART [9].

Adherence is key to achieving efficacy, and therefore also key to cost-effectiveness. Development of interventions to support adherence will benefit patients in terms of outcomes, health services in terms of cost, and public health in terms of onward transmission of HIV.

In spite of increasing evidence for the effectiveness of PrEP and models showing cost-effectiveness, this does not always relate to affordability. The main limiting factor in terms of affordability remains the price of the drugs [26,27], which will reduce as these drugs come off patent in the coming years.

Health systems

In the UK, there is a well-established sexual health service, which is an ideal setting for delivering PrEP. However, this is not replicated in health systems in other countries. For example, women in the US may receive sexual health services from gynaecologists, and infection disease practitioners often treat people only when they are HIV positive, so HIV-negative MSM and TGW may fall between services. There is no clear pathway for PrEP within the US health system which may lead to fragmented service provision and which can already be observed in the wide range of specialties that have been prescribing PrEP in the US since approval [18].

Conclusion

In this new and emerging area of research, long-term data are lacking. PrEP remains controversial to some and has yet to be licensed in the UK. There remain some issues that need to be resolved, including cost-effectiveness, resistance and potential toxicity. However, evidence on the efficacy of PrEP is compelling.

Table 1. Summary of the results of 10 randomised controlled trials of oral PrEP

Study ID	Study design			Adherence	Incidence of HIV	Efficacy		Resistance
	Total	Intervention	Control			mITT efficacy	On-treatment efficacy	Resistance in cases observed per group
	n, study site(s)	(n enrolled)	(n enrolled)	(according to outcome measures reported)	Total cases (of which, PHI at enrolment) Per group cases (mITT) excluding PHI	Relative reduction in incidence (and alternative efficacy measures if relative reduction not reported)		PHI at enrolment n resistant/n cases (%) Post-enrolment transmission n resistant/n cases (%)
MSM–TGW								
iPREX 2010 [6]	n=2,499 Peru, Ecuador, South Africa, Brazil, Thailand and USA	TDF–FTC (1,251)	Placebo (1,248)	Self-reported: 95% Detectable drug: 51%	Total: 110 (10) TDF-FTC: 36/1,224 (2.94%) Control: 64/1,217 (5.26%)	TDF-FTC: 44%	92% for those with detectable drug levels	For PHI at enrolment: TDF-FTC: 2/2 (100%) Placebo: 1/8 (12.5%) For post-enrolment transmission: TDF-FTC: 0/36 (0%) Placebo: 0/64 (0%)
US MSM safety trial 2013 [7]	n=400 USA	1: immediate TDF (101) 2: delayed TDF (100)	1: immediate placebo (99) 2: placebo delayed (100)	Pill count: 92% Pill bottle opening: 77%	Total 7 (1) Immediate TDF: 0/101 (0%) Delayed TDF: 3/100 (3%) (prior to starting TDF) Immediate placebo: 0/99 (0%) Delayed placebo: 3/100 (3%) (prior to starting placebo)	Unable to calculate relative reduction as 0 cases in intervention group	Not reported	PHI at enrolment: Placebo: 1/199 (0.5%) (unclear if IMM or delayed) Post-enrolment transmission: TDF IMM: 0/101 (0%) Placebo IMM: 4/99 (4.01%) TDF delay: 0/100 (0%) Placebo delay: 3/100 (3%)
IPERGAY 2015 [4]a	n=414 France and Canada	TDF-FTC (206) Event–driven dosing	Placebo (208)	Self-reported correct use: 45% in TDF-FTC, 40% in control	Total: 16 (0) Intervention: 2/199 Control: 14/201	TDF-FTC: 86% NNT to prevent infection: 18	Not reported	Not reported
PROUD 2015 [5]b	n=545 UK	Immediate TDF-FTC (276)	Deferred TDF-FTC (269)	56% of participants had drugs prescribed for 86% of FU days	Total: 22 (6) Immediate: 3/267 Deferred: 19/256	TDF-FTC: 86% NNT to prevent 1 infection: 13	Not reported	PHI at start of PrEP: 3/6 (50%) Post-enrolment transmission: Resistance test results not reported
Heterosexual								
Peterson West African 2007 [10]	n=536 Ghana, Cameroon and Nigeria	TDF (469)	Placebo (567)	Pill count: 69%	Total: 8 TDF: 2/427 Placebo: 6/432	TDF: 66%	No reported	Resistance tests completed and no cases identified, but only 1 sample was tested (1 of the TDF group).
Partners PrEP 2012 [9]	n=4,758 Kenya and Ugandac	1: TDF (1,572) 2: TDF-FTC (1,568)	Placebo (1,568)	Pills dispensed: 98% Pill count: 92% Detectable drug: 82%	Total: 96 (14) TDF: 17/1,584 TDF-FTC: 13/1,579 Placebo: 52/1,584	TDF: 67% TDF-FTC: 75%	90% for those with detectable drug levels	For PHI at enrolment: TDF arm: 2/5 (40%) TDF–FTC arm: 1/3 (33%) Placebo: 0/6 (0%) Post-enrolment transmission: TDF: 2/17 (11.76%) TDF-FTC: 1/13 (7.69%) Placebo: 1/52 (1.92%)

Trial	Intervention	Comparison	Adherence	HIV infections (Total, n)	Efficacy	Drug level / additional	Resistance / comments
Botswana TDF2 2012 [8] n=1,219 Botswana	TDF-FTC (601)	Placebo (599)	Pill counts: 84% (in TDF-FTC and placebo groups) Self-reported: 94% (for both groups)	Total: 47 (3) TDF-FTC: 9/601 Placebo: 35/599	TDF-FTC: 74%	77.9% excluding those 30 days after their last reported dose	Only two resistance tests are reported. Assume other tests were negative, but not described. Not identified as PHI at enrolment or post-transmission enrolment: TDF-FTC: 1/9 (11.11%) Placebo: 1/35 (2.86%)
FEM PrEP 2012 [11] n=2,120 Kenya, South Africa, Tanzania[d]	TDF-FTC (1,062)	Placebo (1,058)	Self-reported: 95% Pill count: 88% Detectable drug: 38%	Total: 70 (2) TDF-FTC: 33/1,062 Placebo: 35/1,058	Authors report: estimated hazard ratio 0.94	Not reported	PHI at enrolment: TDF/FTC: 1 Placebo: 1 Post-enrolment transmission: TDF-FTC: 4/33* Placebo: 1/35 *although in one case it is unclear if PHI at enrolment
VOICE 2013 [12] n=5,029 South Africa, Uganda, Zimbabwe[e]	1: TDF oral (1,007) 2: TDF-FTC oral (1,003) 3: 1% TDF topical vaginal gel (1,007)	1: Oral placebo (1,009) 2: topical placebo (1,003)	Reported and pill count: 84–91% Undetectable in Oral TDF: 58% Oral TDF-FTC: 50%	Total: 322 (22) Oral TDF: 52/993 Oral TDF-FTC: 61/985 Topical TDF 1%: 61/996 Oral placebo: 60/999 Topical placebo: 61/996	Reported by the authors hazard ratio: TDF: –49% TDF-FTC: –4%	Not reported	PHI at enrolment: (21) Oral TDF: 0/5 Oral TDF-FTC: 3/9 Oral placebo: 0/1 Topical TDF 1%: 0/4 Topical placebo: 0/3 Post-enrolment transmission: 301 Oral TDF: 0/58 Oral TDF-FTC: 1/55 Oral placebo: 0/60 Topical TDF 1%: 0/60 Topical placebo: 0/68
People who inject drugs							
CDC4370 BTS [13] n=2,413 Bangkok, Thailand	TDF (1,204)	Placebo (1,209)		Total: 52 (2) Intervention: 17/1,204 Control: 33/1,207	TDF: 52%	Detectable drug: 73.5%	Resistance tests completed and no cases identified

PHI: primary HIV; mITT: modified intention to treat; IMM: immediate; FU: follow up; NNT: number needed to treat

a Interim analysis recommended discontinuation of the placebo arm and that on–demand PrEP be offered to all participants

b Interim analysis of the PROUD study data has shown that pre-exposure prophylaxis (PrEP) is highly protective and participants in the deferred arm should have the intervention

c Trial stopped after interim analysis indicated efficacy for both intervention arms, hence placebo group discontinued

d Trial stopped after interim analysis indicated unlikely to detect difference; 33% did not complete the study per protocol

e TDF oral and TDF topical arms stopped after interim analysis indicated futility

The bottom line in HIV prevention is knowing your HIV status; wide access to testing needs to be available for all. Regular testing and counselling must be provided alongside PrEP in order to ensure that it is effective. If this is achieved, and PrEP is delivered in conjunction with other HIV prevention strategies, then PrEP has the potential to make a real impact on the HIV epidemic.

Conflicts of interest

EP and EY declared no conflicts of interest.

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