

# HIV pre-exposure prophylaxis (PrEP): effective but controversial

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Pre-exposure prophylaxis or PrEP has been shown to be effective in certain groups at reducing the acquisition of HIV. Despite its efficacy, the NHS appears reluctant to fund its use. In this article the authors describe PrEP and discuss some of the pros and cons of its use.

In 1981, cases of a rare lung infection known as *Pneumocystis carinii pneumonia* (PCP) were reported in five young, previously healthy, gay men in Los Angeles.<sup>1</sup> This marked the beginning of the HIV/AIDS pandemic, during which an estimated 70 million people have been infected and 35 million have died.<sup>2</sup> A diagnosis of HIV was effectively a death sentence until 1995, when the first protease inhibitor was introduced. This ushered in a new era of highly active antiretroviral therapy (HAART) and started a revolution in the fight against HIV.

These days, if treated with effective antiretroviral therapy (ART), people living with HIV can expect a similar life expectancy to the HIV-negative population. In addition, when ART fully suppresses the HIV viral load, it becomes almost impossible for an HIV-positive individual to transmit the virus to an uninfected sexual partner.<sup>1</sup>

Despite this, there were 6095 new diagnoses of HIV in the UK in 2015. 75% of



Figure 1. Despite public education around HIV and use of condoms, there were 6095 new diagnoses of HIV in the UK in 2015; 75% of these new infections occurred in men (© KTSDesign/Science Photo Library)

these new infections occurred in men, and men who have sex with men (MSM) were disproportionately affected, accounting for 56% of new infections. Condoms have traditionally been the mainstay of HIV prevention and are highly effective when used correctly and consistently. However, 95% of new infections were due to people having sex without a condom, and it is therefore unlikely that HIV can be controlled with condom promotion alone.<sup>3</sup> Pre-exposure prophylaxis (PrEP) is one potential answer to the problem.

## WHAT IS PrEP?

ART medicines are already used as 'PEP' or post-exposure prophylaxis to reduce the

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chance of HIV acquisition following an exposure event. PEP has been described conceptually as a 'morning-after pill' for HIV. PrEP is the use of ART by an HIV-negative person before sex to prevent acquisition of HIV and can be thought of more as a 'contraceptive pill' for HIV.<sup>4</sup>

PrEP usually consists of a combination of tenofovir with emtricitabine (Truvada). Most of the evidence concerns daily PrEP dosing; however, a regimen known as 'event-based dosing' allows a more flexible use of PrEP based on sexual activity, and has the potential to be more cost-effective. In the French IPERGAY study, an 86% reduction in HIV acquisition was seen in those taking a double dose of PrEP (*ie* two pills) before having sex, then single doses of PrEP every day for each day that the participant continued having sex without a condom. A single dose was taken on the day after the last risk exposure. For someone who was only at risk from one sexual encounter a month, this would be

considerably different compared to daily PrEP. For a person who was sexually active more than once a week, their dosing would approach daily PrEP.<sup>5</sup>

#### EVIDENCE FOR PrEP

In recent years, a multitude of PrEP randomised controlled trials have been going on around the world in different populations, including MSM, HIV serodiscordant couples, women, transgender women, commercial sex workers and injecting drug users, as shown in Table 1. It is clear that PrEP is highly effective at preventing HIV transmission if taken as directed. Most of the trials have been placebo-controlled, whereby the use of placebo aimed to minimise confounding due to 'risk compensation'; that is, individuals on PrEP potentially engaging in riskier sexual practices due to their perceived protection.

A recent study in the UK, the PROUD study, aimed to demonstrate the true effectiveness of PrEP, any sexual behaviour

change because of PrEP, and realistic levels of adherence. Researchers recruited HIV-negative MSMs who had had anal intercourse without a condom in the past 90 days. They were randomly allocated to receive daily PrEP, either immediately or after a one-year deferral period.

The main finding of the PROUD study was that HIV incidence was reduced by 86% for those on PrEP compared to those in the deferral group (90% CI 64–96). This means that to prevent one new HIV infection, you would have to treat 13 men of a similar population with PrEP for one year. This finding was considered to be so significant that PrEP was offered earlier than planned to the deferral group on ethical grounds. PrEP was also shown to be safe, with no serious adverse events reported. Risk compensation was demonstrated, with participants who received PrEP immediately more likely to have had receptive anal sex without a condom with 10 or more partners than the deferral group. However, there

Study name	PrEP regimen, dosing and comparator	Study population	Adherence level	Location	Efficacy
VOICE <sup>8</sup>	Daily tenofovir or daily Truvada vs placebo	Women	30%	South Africa, Uganda, Zimbabwe	No reductions in HIV infection, likely due to poor adherence
FEM-PrEP <sup>9</sup>	Daily Truvada vs placebo	Women	37%	Tanzania, South Africa, Kenya	Study stopped early because of lack of efficacy related to poor adherence
Partners <sup>10</sup>	Daily tenofovir or Truvada vs placebo	HIV sero-discordant couples	81%	Kenya, Uganda	62% reduction in tenofovir arm; 73% reduction in Truvada arm
TDF2 <sup>11</sup>	Daily Truvada vs placebo	Heterosexual men and women	80%	Botswana	62% reduction in infections
iPREX <sup>12</sup>	Truvada or placebo	MSM	51%	Brazil, Ecuador, South Africa, Thailand, USA	73% reduction in those taking PrEP >90% of time (but 44% efficacy overall)
PROUD <sup>6</sup>	Daily Truvada vs no PrEP	High-risk MSM	56–86%	UK	86% reduction in HIV transmission
IPERGAY <sup>5</sup>	Event-based Truvada vs placebo	High-risk MSM		France	86% reduction in HIV transmission

Table 1. Key studies of PrEP in different populations

was no corresponding difference in sexually transmitted infections. The study also demonstrated the feasibility of delivering PrEP as part of routine sexual health services.<sup>6</sup>

The evidence for PrEP is strong. WHO now recommends that anyone with a 'substantial risk' of HIV should be offered PrEP as part of a comprehensive prevention package.<sup>7</sup> The USA, Canada, France and South Africa all now provide PrEP; and in October 2016, Norway became the first country to offer PrEP free of charge.<sup>4</sup>

### SITUATION IN THE UK

In the wake of the PROUD study, many clinicians, sexual health organisations and people in 'at risk' groups in the UK have been eagerly awaiting the roll out of PrEP. However, in March last year, NHS England announced that they would not provide PrEP, and that local authorities should be the responsible commissioners for any preventative interventions. NHS England is the only commissioner with experience of purchasing antiretroviral medicines and does commission other preventative interventions. Cash-strapped local authorities were not keen to pick up the tab. Following a legal challenge by the National AIDS Trust, it was ruled that NHS England does have the ability, but not the obligation, to commission PrEP. However, on 4 December 2016, it announced that it plans further research instead of implementation. Therefore, at present, there is no way of obtaining PrEP on the NHS.<sup>4</sup>

Anyone who wants to use PrEP must either obtain a private prescription or purchase drugs over the internet. This can cost anywhere from £40 per month for generic drugs produced outside the European Union, to £400 per month for branded Truvada. The community advocacy website [www.iwantprepnw.co.uk](http://www.iwantprepnw.co.uk) provides information on PrEP and links to vendors who have been validated with therapeutic drug level monitoring (measuring plasma

drug concentrations). Many sexual health services are 'PrEP supportive' and will provide advice and monitoring of renal function for those taking PrEP to ensure no renal toxicity from tenofovir.<sup>4</sup>

The lifetime cost of managing HIV is high (£360 800 per patient).<sup>4</sup> PROUD found that only 13 individuals needed to take PrEP to prevent one infection; researchers therefore believe that PrEP is likely to be cost-effective, particularly in those reporting more than five casual partners in the last year, or once patents expire and drug costs are reduced.<sup>6</sup>

The British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH) strongly recommend that PrEP be made available within a comprehensive HIV prevention package to:

- MSM, trans men and trans women who are engaging in condomless anal sex
- HIV-negative partners who are in serodiscordant heterosexual and same-sex relationships with an HIV-positive partner whose viral replication is not suppressed
- Other heterosexuals considered to be at high risk.<sup>13</sup>

### CONTROVERSIES WITH PrEP

There are many criticisms of PrEP as an HIV prevention strategy, one of the most prominent being that of risk compensation. Will people stop using condoms consistently and engage in riskier sex that outweighs the protective benefit of PrEP? The PROUD study was designed to address these concerns. Risk compensation was demonstrated in the PROUD study, with participants who received PrEP more likely to have had receptive condomless anal sex with 10 or more partners than those not on PrEP. However, there was no corresponding difference in sexually transmitted infections between groups.<sup>6</sup>

Although reassuring, the PROUD study was originally designed to look at changes

in sexual behaviour in every individual participant with in-depth questionnaires. However, the majority of participants did not complete these and therefore we should question the validity of the conclusion that there was minimal risk compensation. Furthermore, the trial in its original form was stopped early, increasing the chance of type one error: if more time had passed would we have seen an increase in risk compensation or a decrease in adherence and effectiveness of PrEP? And even if PrEP does result in riskier sex, does that mean it should not be used? Many would argue that withholding PrEP is a moralistic judgment, and compare the advent of PrEP with the introduction of the oral contraceptive pill in the 1960s and the sexual liberation that followed.

Another important consideration is the role PrEP might play in the development of drug resistance. Drug resistance could mean losing important first-line medicines, thus increasing the financial burden on the NHS and having potentially catastrophic consequences for low-income countries. The greatest danger is starting PrEP in those who have undiagnosed early HIV infection, as resistance can quickly evolve. This is a risk in people buying PrEP from a website, where testing is not conditional before starting. The baseline HIV test should ideally be a fourth-generation (combined antigen/antibody) test that would pick up early infection.<sup>4</sup>

PrEP is not without its health risks either. Tenofovir causes renal tubular toxicity and a reduction in bone mineral density.<sup>4</sup> These have been shown to be reversible following cessation of tenofovir; however, there is an ethical dilemma in prescribing these drugs to otherwise healthy individuals.

### CONCLUSIONS

What is clear is that people are using PrEP in the absence of NHS provision. This means inequity, in that many of the most vulnerable members of society do not have access to it due to its cost. It also means

## KEY POINTS

- PrEP is a useful HIV prevention tool for highly sexually active MSM and HIV serodiscordant couples
- It is highly likely that PrEP will become an important component of HIV prevention and that pressure from advocacy groups will force NHS England to provide it free of charge
- It is therefore important to be familiar with PrEP as more and more MSM are likely to be using it
- Patients may ask about PrEP, in which case they should be directed to sexual health clinics for an in-depth discussion about daily versus event-based dosing, HIV testing, baseline creatinine and follow-up urinalysis
- Patients on PrEP may be at risk of other sexually transmitted infections
- Tenofovir causes renal impairment and reduction in bone mineral density
- If PrEP needs to be stopped for any reason, doctors should counsel patients regarding condom use and consider consulting a GUM/HIV specialist

that PrEP is not being offered with support, which is crucial to its effectiveness.

Existing HIV prevention strategies are failing to curb the epidemic and there were 6095 new diagnoses of HIV in the UK in 2015.<sup>3</sup> PrEP is an exciting new HIV prevention tool that is highly effective at preventing HIV transmission, provided it is taken properly. It is likely that pressure from advocacy groups will force NHS England to provide PrEP free of charge, but at present PrEP users obtain it from private providers or the internet. It is critical that those interested in PrEP have a negative HIV test immediately prior to starting PrEP. They should therefore be directed to sexual health services for HIV testing, STI screening, baseline creatinine and monitoring.

**Declaration of interests:** none declared.

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