Why we need a pre-exposure prophylaxis (PrEP) trial among gay men in the UK

We need new HIV prevention methods

We do have effective ways to reduce the transmission of HIV, including risk reduction counselling and provision of condoms. When condoms are used consistently, they are highly effective.

Despite the availability of these prevention methods, the number of new infections each year in the UK is rising, with more than 3,800 new infections in 2010. Gay men have the highest risk of becoming infected in the UK, and new diagnoses of HIV have increased by 70% in the last ten years.

Risk reduction counselling and condoms are not sufficient to control the epidemic, partly because not everyone at risk uses condoms every time they have sex. New ways of reducing the risk of HIV are needed, in addition to those we already have, to help those at highest risk of HIV protect themselves.

Pre-exposure prophylaxis (PrEP)

PrEP is a HIV prevention strategy that involves HIV-negative people taking antiretroviral drugs (ARVs) to reduce the risk of becoming infected if they are exposed to the virus. It involves taking the drugs regularly enough to ensure there is a high enough concentration in the tissues to stop the virus from replicating and becoming an established infection.

Truvada (tenofovir-emtricitabine) is the drug that is most widely used for PrEP at the moment. Truvada PrEP is taken every day and can have side effects. Because of this, PrEP may not appeal to gay men who rarely have unprotected sex, or who only have one partner, but it may be a useful option for people who are highly sexually active and do not or cannot always use condoms.

We expect PrEP to be part of a package of methods to reduce HIV (including risk reduction counselling and condom distribution), rather than a stand-alone strategy.

The evidence on PrEP

Effectiveness

There have been a number of trials looking at whether PrEP can protect people from HIV. Four trials, involving a total of 8,916 participants, compared Truvada to a placebo; one also compared another drug to placebo. One of the four did not find that this drug reduced HIV infections, with the lack of effectiveness seeming to be linked to poor adherence. Nonetheless, the overall evidence that Truvada safely reduces the risk of HIV infection was sufficient to persuade the US Food and Drug Administration to approve the use of this drug for PrEP.

Only one of these trials (the iPrEx trial) looked at whether PrEP could reduce infections for gay men. iPrEx found that daily Truvada PrEP reduced the risk of HIV infection by 42% compared to a placebo.

Key points

- We need new HIV prevention methods, as 3000 gay men are diagnosed with HIV in the UK each year.
- Trials have shown that Pre-exposure prophylaxis (PrEP), which involves HIV-negative people taking antiretroviral pills, can substantially reduce their risk of HIV infection, but only if the pill is taken regularly enough (currently daily).
- Modelling studies suggest that, if targeted at people at high risk of HIV infection, PrEP is cost-effective, even by the strictest criteria. We need to explore whether these findings are true in the UK.
- We do not know whether gay men in the UK will take PrEP, and if they do, what effect this will have on their sexual risk behaviour.
- We need a large trial to help answer these questions, and provide guidance to UK policymakers on whether PrEP works and is cost-effective in this context. The PROUD study is a pilot to see if such a trial would be possible.
Adherence

The evidence on PrEP suggests that adherence to the drugs is crucial for preventing infection. Measuring the drug levels in their blood was a much better predictor of protection and revealed that people overreport their adherence when you ask them about it. In iPrEx, measuring drug levels showed that 49% of trial participants had not been taking PrEP at all; in those whose drug levels showed they had been taking PrEP daily, it reduced the risk of HIV infection by at least 92% compared to a placebo.

Safety and side-effects

The trials so far have not found that PrEP caused serious side-effects. A small number of participants receiving Truvada have developed abnormalities in the markers used to monitor kidney function but these reversed when they stopped taking the drug. PrEP with Truvada did cause nausea and vomiting in the first 12 weeks in about 10% of participants.

Risk behaviours

One of the concerns relating to PrEP is that if people think the drugs they are taking protect them from acquiring HIV, they may engage in riskier sexual behaviour (eg. be less likely to use a condom), increasing their risk of being exposed to HIV. The trials conducted so far have found no evidence that taking PrEP (or a placebo) led to riskier behaviour. However, this needs to be treated with caution as the trials were placebo controlled, so participants did not know if they were receiving an active drug, and it was not known at that stage if PrEP was effective.

Cost-effectiveness

PrEP is expensive, but so is treating HIV, which makes reliable information on the cost-effectiveness of PrEP essential. For each case of HIV infection prevented, an estimated £280,000 - £360,000 in lifetime treatment costs could be saved. A modelling study based on the iPrEx trial results from Lima, Peru found that if targeted at people at high risk of HIV, PrEP was highly cost effective, costing from US $140 to $1400 per disability-adjusted life year with HIV averted, according to who was targeted and what their adherence rates were.

Some other modelling studies have estimated the cost-effectiveness of PrEP, and also found that its cost effectiveness depends on only giving it to people at high risk.

Resistance

There are concerns that the use of antiretrovirals to prevent HIV could lead to the development of resistance to these drugs. If people become infected while on PrEP, or start on PrEP when already infected. Mathematical models have found that ARV resistance could develop if people on PrEP are not monitored systematically for HIV. No one who was infected with HIV during the iPrEx study developed drug resistance, but two people who accidentally joined the trial just after becoming infected, but before they could be tested, developed resistance to FTC.

PrEP and Treatment as Prevention

Another important new HIV prevention strategy is treating people who are HIV positive as early as possible after infection, as ART can suppress the levels of virus, making them much less likely to transmit the disease.

The HPTN052 study found that treating the HIV-positive partner reduced the risk of the HIV-negative partner becoming infected by them by 96%. In the context of stable discordant couples this is a very promising strategy, provided couples are monogamous; it is worth noting that about a quarter of infections caught in HPTN052 came from other sexual partners.

There is also indirect evidence from places ranging from Denmark to South Africa that HIV treatment reduces HIV infections in a population if it reduces viral load in a sufficiently high proportion of HIV positive people.

So far, however, this does not seem to be happening in the UK, probably because a high proportion of HIV is transmitted by people unaware of their status. The success of Treatment as Prevention is reliant on people knowing their HIV status soon after infection with the virus. It does not protect individuals from infection from someone who does not know their HIV status, which is the case for a large proportion of HIV-positive gay men in the UK. In this situation, PrEP may empower HIV-negative MSM to protect themselves against infection, without depending on their sexual partners knowing their status, adhering to treatment or using condoms.

What the PROUD trial will do

While there is no doubt that PrEP can reduce the risk of acquiring HIV, there are still important questions that need to be answered before deciding whether PrEP should be offered to gay men in the UK.

The Medical Research Council Clinical Trials Unit (MRC CTU) and the Health Protection Agency are working with NHS clinics to undertake a pilot study, to see if it would be possible
to carry out a full trial of PrEP among gay men in the UK, to answer questions such as:

- Do gay men at high-risk of HIV want PrEP?
- How adherent will they be to taking tablets daily?
- How will being on PrEP affect their numbers of partners, use of condoms and other risk behaviours?
- How effective, and how cost-effective, is PrEP at reducing risk of HIV among MSM in the UK?

**Conclusions**

We need new ways to prevent HIV in gay men in the UK, and reverse the rise in new infections. We already know that PrEP can reduce the risk of HIV for some high-risk people, but this depends on adherence and sexual risk behaviours. Treating those who are HIV-positive as soon after infection as possible can also reduce transmission, but depends on early diagnosis.

It is not yet known whether PrEP will be effective and cost-effective for preventing HIV among gay men in the UK, but the evidence so far shows that it can be effective in other settings. PrEP could be a useful additional weapon in the fight against HIV. If the pilot study is successful and the PROUD trial takes place, it will help to answer some of the important questions that remain. It will provide evidence to inform decisions on whether PrEP should be made available on the NHS for gay men at high risk of HIV.

**Recommended reading**

Goicochea, P. iPrEx Fact Sheet: Key Results. 2010 [cited 2012 14/09/2012]; Available from: http://www.iprexnews.com/studyresults/pdfembargo/englishversion/iPrEx%20Fact%20Sheet%20Key%20Results%20Final%20PE.pdf


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