PrEP

This briefing paper provides an overview of pre-exposure prophylaxis (PrEP) for people planning, commissioning or providing HIV prevention activities in the UK. It does this by reviewing thirty key questions about PrEP and how it might be implemented in the UK.

What is PrEP?

Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy that uses antiretroviral drugs to protect HIV-negative people from HIV infection. People take antiretrovirals (ARVs) when they are at risk of exposure to HIV, in order to lower their risk of infection.

Research suggests that PrEP is highly efficacious in preventing the sexual transmission of HIV, as long as the drugs are taken regularly, as directed. However, PrEP does not prevent other sexually transmitted infections or pregnancy.

PrEP is one of several ways in which antiretroviral drugs can be used to prevent HIV transmission:

- ARVs given to an HIV-negative person before possible exposure to HIV: pre-exposure prophylaxis (PrEP).
- ARVs given to an HIV-negative person *after* possible exposure to HIV: post-exposure prophylaxis (PEP).
- ARVs taken by an HIV-positive woman during pregnancy and childbirth: prevention of mother-to-child transmission (PMCT).
- ARVs taken by an HIV-positive person: treatment as prevention (TasP).

How does PrEP work?

The principle of PrEP is similar to that of antimalarial tablets used to prevent malaria when travelling in tropical countries.

Somebody who does not have HIV takes enough antiretrovirals (ARVs) for there to be high levels of the drugs in their bloodstream, genital tract and rectum before any exposure to HIV. If exposure occurs, the ARVs stop the virus from entering cells and replicating. This prevents HIV from establishing itself and the person remains HIV negative.

The antiretrovirals which are currently used as PrEP (*Truvada*, a pill containing two drugs, tenofovir and emtricitabine) were chosen because they have limited side-effects, have few problems with drug resistance, reach high levels in the genital tract and rectum, and remain in the body for a relatively long time.

Although the term PrEP is often used to refer to ARVs in oral tablets, other delivery methods are possible. A vaginal ring, or a microbicide gel that is placed in the vagina or rectum, can provide ARVs – the approach is sometimes called 'topical' PrEP. However, so far studies of microbicide gels for women have not been successful, largely due to social barriers and poor adherence.

Why is PrEP needed when effective prevention methods are already available?

Male and female condoms, when used consistently and correctly, are highly effective against HIV. Moreover, a diverse range of behavioural interventions have been implemented since the 1980s. Despite this, there are thousands of new HIV infections every year.

The extremely high rate of infections seen in PrEP studies shows the urgency of improving HIV prevention. In the PROUD study, 9% of gay men who did not receive PrEP became HIV positive within a year. For this sub-group of gay men, existing prevention interventions clearly are not sufficient. PrEP has the potential to prevent new infections among some of those at greatest risk of acquiring HIV.

Although condoms work well for many people, describing them as the only acceptable method of HIV prevention is not helpful. PrEP gives clinicians and HIV prevention workers an additional option that will be appropriate for some, but not all, people. Individuals may need different HIV prevention options for different periods of their lives as their circumstances change.

How effective is PrEP?

When considering PrEP for men who have sex with men in the UK, the most relevant data come from the PROUD study, which was conducted in England and reported its results in 2015. (See graphic.) Men who took part in the PROUD study were at higher risk of HIV infection than many other gay men. They frequently reported multiple partners, inconsistent or irregular condom use,

PrEP

PROUD study

Over 500 men who have sex with men enrolled.
Recruited at 13 English sexual health clinics. Most used condoms some, but not all, of the time. Many had multiple sexual partners and were at higher risk of HIV infection than some other men.

Random allocation

Intervention group
268 participants: immediate PrEP

PrEP is a daily tablet of *Truvada* (tenofovir and emtricitabine). Participants knew it was effective and that they were taking it.

Appointments for STI check-ups and safer sex advice every three months.
Follow-up for one year.

13 participants stopped taking PrEP because of side-effects but 12 started it again.

3 men acquired HIV (incidence 1.2%)
These men were probably not taking PrEP at the time. Two had dropped out of the study. One probably got HIV just before starting PrEP.

Men in this group will receive PrEP until April 2016.

Control group
255 participants: no PrEP

Men in the control group could get PrEP after one year's wait.

Appointments for STI check-ups and safer sex advice every three months.
Follow-up for one year.

Broadly similar sexual behaviour and identical rates of STIs in the two groups.

20 men acquired HIV (incidence 9.0%)

All men in the control group have now been offered PrEP and can get it until April 2016.

recreational drug use, sexually transmitted infections (STIs) and use of post-exposure prophylaxis (PEP). However, any man who does not always use a condom with male partners was eligible to take part.

In the control group of men not receiving PrEP, there were 20 HIV infections. In the group of men offered PrEP, there were 3 HIV infections, each in a man who was probably not actually taking PrEP at the time.

Comparing the two groups, PrEP reduced the number of infections by 86% (credible range: 64-96%). This surpasses the real-life effectiveness of consistent condom use. One HIV infection was prevented for every 13 men given PrEP.

A wide range of results have been reported in other PrEP studies, with some finding high effectiveness and some none at all. (See table.) The crucial factor determining effectiveness is adherence, in other words whether people actually use PrEP regularly, without missing too many doses.

In studies in which many participants had poor adherence, PrEP had no benefit at all. This was the case in several studies with young women in African countries.

But where adherence has generally been good, PrEP has been shown to be effective. This includes studies with men who have sex with men and with serodiscordant couples in east Africa. Even in studies whose headline findings were that PrEP was ineffective, individuals who used PrEP regularly had greater protection.

If programmes recruit individuals who are motivated to take PrEP and help them with adherence, PrEP is likely to be highly effective.

How does PrEP's effectiveness compare with that of other interventions?

When HIV-positive people start HIV treatment, it reduces infections to heterosexual HIV-negative partners by 96%. Other than this, a reduction of HIV infections by 86% surpasses that of most other HIV prevention interventions that have been tested in randomised controlled trials, many of which have failed to demonstrate any benefit. Moreover, the evidence of effectiveness for many behavioural interventions (such as groupwork and social marketing campaigns) relates mostly to short-term changes in sexual behaviour which do not necessarily lead to reductions in infections. When HIV incidence has been assessed, behavioural interventions have on average reduced infections by 46%.

Condom use has not been tested in randomised control trials. However, observational studies suggest that people who say they consistently use condoms have around 80% fewer HIV infections (in heterosexuals) or around 70% fewer infections (in men who have sex with men) than people who never use them.

Is PrEP effective for heterosexual men and women?

While several studies have found oral PrEP to be effective for men who have sex with men, studies offering PrEP to heterosexual men and women have had mixed results. All these trials were conducted in African countries, with some testing vaginal gels rather than pills. (See table.)

In three studies, heterosexual men and women given PrEP had between 39 and 75% fewer HIV infections. But in three others, women given PrEP had as many HIV infections as women receiving a placebo.

Individuals who used PrEP regularly were more likely to remain HIV negative than others.

But adherence has been very poor in some trials conducted in African countries. There were social barriers to taking PrEP, including women's position in society, personal relationships, HIV stigma and ambivalence about the research process. The studies with the most disappointing results were done with young, mostly single women. Good adherence was achieved in a study recruiting heterosexual couples in which one partner was living with HIV.

This does not mean that PrEP can never be an appropriate prevention technology for women. The circumstances of heterosexual men and women in the UK who need to protect themselves from HIV are likely to be different from those of the people who took part in the African studies. PrEP may be a viable option for some heterosexuals in the UK.

But there may also be biological factors which could make PrEP less effective for women. Researchers have found that after a single dose of PrEP, concentrations of tenofovir are much lower in the vagina and cervix than they are in the

Key PrEP studies

Study	Results announced	Population	Number of participants	PrEP agent	Reduction in infections
CAPRISA 004	2010	Women, 18-40 years, South Africa	889	Tenofovir vaginal gel (intermittent dosing)	39%
iPrEx	2010	MSM and transgender women, international	2499	*Truvada* pill	44%
FEM-PrEP	2011	Women, 18-35 years, Africa	1950	*Truvada* pill	0%
Partners PrEP	2011	HIV-serodiscordant couples, Kenya and Uganda	4758	*Truvada* pill or tenofovir pill	75% on *Truvada*; 67% on tenofovir
TDF-2	2011	Heterosexual men and women, 18-35 years, Botswana	1200	*Truvada* pill	63%
VOICE	2012	Women, 18-45 years, Africa	5029	Tenofovir vaginal gel, tenofovir pill, or *Truvada* pill	0%
Bangkok tenofovir study	2013	Men and women who inject drugs, Thailand	2413	Tenofovir pill	49%
FACTS 001	2015	Women, 18-30 years, South Africa	2059	Tenofovir vaginal gel (intermittent dosing)	0%
IPERGAY	2015	MSM and transgender women, France and Canada	400	*Truvada* pill (intermittent dosing)	86%
PROUD	2015	MSM and transgender women, England	544	*Truvada* pill	86%

Note: *Truvada* pills contain two drugs, tenofovir and emtricitabine.

rectum. The implication would be that women may need to maintain near-perfect adherence to have protection against HIV during vaginal sex, whereas a lower level of adherence may be protective during anal sex. More research on this topic is needed.

Recommendations on providing PrEP to heterosexual men and women are included in American guidelines. For a serodiscordant couple aiming to conceive a child, PrEP may be used alongside HIV treatment for the positive partner.

How soon after starting daily PrEP is it effective?

Protective levels of *Truvada* are usually reached in rectal tissue and blood after between four and seven daily doses. These results are most relevant for gay men. Because of the lower concentrations of tenofovir in the vagina and cervix, it may take PrEP longer to protect women, perhaps requiring three weeks of daily doses.

How adherent do people need to be for PrEP to be effective?

By testing participants' blood for the presence of PrEP drugs, researchers have attempted to estimate the number of PrEP doses they have actually taken. They have then looked at the number of HIV infections in people with different levels of adherence.

For example, in the iPrEX OLE study of men who have sex with men and transgender women most infections occurred in people taking less than two doses a week, with none occurring in individuals taking four or more doses. The researchers calculated the following levels of protection:

- Less than two doses a week: 44% fewer infections (credible range: -31 to 77%)
- Two or three doses a week: 84% fewer infections (credible range: 21 to 99%)
- Four or more doses a week: 100% fewer infections (credible range: 86 to 100%).

These results are relevant to HIV exposure during anal sex, but not vaginal sex. Moreover, there are limitations to the methods used to produce these estimates, so they should be treated with caution. In particular, note that the 'true' figure for the reduction in infections associated with four or more doses could be as low as 86%. It is not necessarily 100%.

But in practical terms, adherence is most important during periods of exposure to HIV. If an individual knows for sure that they are not going to have sex for a period of time, or not with anyone who could expose them to HIV, then they may prefer to stop taking PrEP during that period. However, it may take several days after PrEP is resumed for protective concentrations to build up in tissues.

Factors associated with good adherence in studies include older age, higher levels of education, perceiving oneself to be at risk of HIV infection and having a higher level of sexual activity. While high-quality adherence counselling is probably helpful, we know little about which approaches are most effective.

Must PrEP be taken daily? Can intermittent dosing be effective?

Almost all PrEP studies, including PROUD, asked participants to take PrEP every day. But one study has shown that PrEP pills can also be very effective when people only take it before and after they have sex. This is sometimes known as 'intermittent' dosing or 'event-driven' dosing.

In the IPERGAY study, participants were told to take a double dose of *Truvada* (two pills) from 2-24 hours before anticipated sex, and then, if sex happened, two separate doses in each of the two days that followed.

The study was conducted in France and Canada, recruiting 400 men who have sex with men. As with the PROUD study, many had multiple sexual partners and were at higher risk of HIV infection than many other gay men.

The rate of new HIV infections was 0.9% in the PrEP group and 6.8% in the placebo control group, with the difference translating to an effectiveness of 86% (credible range: 39 to 98%). Extraordinarily and coincidentally, this was the same level of effectiveness as seen in PROUD.

The study demonstrates that good adherence to intermittent PrEP is possible and that it can be as effective as daily PrEP. The researchers calculated that 18 men needed to take PrEP to prevent one HIV infection in a year.

Some participants had sex quite frequently and were

therefore taking PrEP on an almost daily basis. A minority of participants only took a handful of pills a month, either because they were not having much sex or because they had poor adherence.

What could be the advantages and disadvantages of intermittent dosing?

An intermittent dosing schedule could be given as an option in future UK clinical guidelines. The approach may make adherence easier for some people, particularly those who have a good idea when they are likely to have sex. (For example, this is the case for some people who use dating apps.) But personal preferences vary – other people may find the routine of daily PrEP easier to remember.

With fewer overall doses, any missed doses will matter far more than in a daily regimen.

As fewer pills are taken, an intermittent approach is likely to be cheaper. For the same reason, it might reduce side-effects.

A study in Thailand, South Africa and the United States is trying to find out which dosing schedules are easiest to adhere to. Some participants take PrEP daily, others follow a schedule similar to the IPERGAY study, while in a third group participants are asked to take PrEP twice a week plus an additional dose within two hours of having sex. Full results will be announced soon.

What are the side-effects of *Truvada*?

As with other ARVs, *Truvada* can cause short-term side-effects including nausea, tiredness, gastrointestinal symptoms and headache. These are typically experienced by up to one-in-ten people during the first few weeks on the drug only.

Truvada was selected for use as PrEP partly because it has relatively few long-term side-effects. Nonetheless, there are some concerns about tenofovir (one of *Truvada*'s components) in relation to reduced kidney function and bone mineral density. These problems have been noted in small numbers of HIV-positive people, especially older people, who have taken tenofovir for several years. They may have less impact on PrEP users, who are likely to be younger and to be on PrEP for shorter periods of time. But these issues should be carefully monitored as PrEP is rolled out over the next few years.

In PrEP studies, use of tenofovir has been associated with small decreases in key measures of kidney function (creatinine clearance and glomerular filtration rate, GFR), affecting up to 2% of participants. These returned to normal when PrEP was stopped, including in one study in which people took PrEP for up to five years. Losses of bone mineral density have been minimal and also appear to be reversible.

What's the risk of drug resistance developing?

When someone has drug-resistant HIV, this means that the HIV in their body has some mutations. Because of the mutations, some anti-HIV drugs may not work well. While a mutation may render one anti-HIV drug ineffective, it will not affect other drugs, which remain effective. Drug resistance can develop when a person has HIV and takes an inadequate amount of anti-HIV drugs (for example, two drugs rather than a three-drug combination, or misses doses).

For people who take PrEP and do not acquire HIV, there is no possibility whatsoever of having drug-resistant HIV.

In theory, if people are not fully adherent to PrEP, become HIV positive, are not diagnosed and carry on taking PrEP, then drug resistance could develop. But only a handful of cases like this have been documented in PrEP studies.

What has been seen are some cases of individuals who started taking PrEP when they were already in the very early stages of HIV infection. Although an HIV test before beginning PrEP is standard practice, a test may miss recent infection due to each test's 'window period'. Nonetheless, not all people who start PrEP while they are in very early infection develop drug resistance and most who do develop resistance to emtricitabine, not to tenofovir. To avoid this occurring, people beginning PrEP should be carefully checked for possible symptoms of seroconversion (e.g. fever, rash).

Does PrEP work against drug-resistant HIV?

Strains of HIV which are resistant to some specific anti-HIV drugs can be transmitted during sex. This raises the

question of whether PrEP would work if somebody taking it were exposed to drug-resistant HIV.

For the moment, this is a theoretical concern. While there is a strain of HIV (known as K65R) which is resistant to tenofovir and could make PrEP ineffective, only 1 in 1000 transmissions of HIV involve virus with this mutation. No cases of PrEP failure due to drug resistance have been documented.

Does PrEP protect against other sexually transmitted infections?

Whereas condoms protect against HIV, gonorrhoea, chlamydia, syphilis, numerous other infections and unwanted pregnancy, PrEP only protects against HIV. (It may also have some impact on herpes simplex virus type 2 and hepatitis B, but this is uncertain). Rates of sexually transmitted infections have remained at high levels in gay men taking PrEP. For example, half the participants in PROUD had gonorrhoea, chlamydia or syphilis while in the study. There have also been a handful of cases of hepatitis C in HIV-negative gay men receiving PrEP.

How might PrEP users change their sexual behaviour?

Does the protection given by PrEP encourage people to use condoms less than before, or to have more sexual partners? Some people have been very concerned by this possibility.

The PROUD study was designed to help answer this question by mimicking real-life conditions in which people receiving PrEP knew they had the active, effective drug – not a placebo.

At the beginning of the study, participants reported an average of ten partners every three months. Most used condoms with some but not all of their partners. Many had recently used PEP and had sexually transmitted infections. The participants therefore had risky sexual behaviour *before* taking PrEP – it was why they felt they needed it.

For most of these men, sexual behaviour remained unchanged throughout the study, whether or not they were receiving PrEP. This suggests that most participants added PrEP to existing risk-reduction strategies, including condom use – they did not replace condoms with PrEP.

However, the sexual behaviour of a minority of men taking PrEP did change. The proportion of participants who reported receptive anal intercourse without a condom with large numbers of sexual partners increased somewhat. Nonetheless, this was not reflected in a higher rate of sexually transmitted infections in those receiving PrEP.

The iPrEx OLE study (which also mimicked real-life conditions) is reassuring on sexual behaviour. Uptake of PrEP was a little higher in people who already had riskier sex, but comparing periods when people were taking and not taking PrEP, there were no differences in terms of self-reported sexual behaviour or sexually transmitted infections.

What do PrEP users say about the experience of taking PrEP?

Interviews with gay men taking PrEP show that they see themselves as being at risk of acquiring HIV and very much want to stay HIV negative. PrEP gives these men a sense of taking control over their sexual lives, with a future HIV diagnosis no longer being inevitable. Participants describe PrEP as providing an extra layer of protection on top of their efforts to use condoms, some or all of the time. The use of PrEP can help reduce fear, panic and guilt during sex, or after particular incidents.

One man said that HIV used to scare him during sex, even when condoms were used:

"*I won't say the anxiety has gone-gone, but it's not in the front of my head as it used to be, where I was obsessively worried about it while sex was happening.*"

Similarly a 29-year old said:

"*It's not like I'm going to go out and being like, 'Ooh, bareback now. I'm protected. It's fine.' It's so, so not the case…I just didn't have the overwhelming stress and fear and guilt that I would have done.*"

PrEP can also affect people's behaviour in unexpected ways:

"*After having been on PrEP I've been a lot more confident and I've been a lot more selective about my partners. I'm not sure if that's to do with PrEP or if that's just a phase I'm going through in life. So I've actually been having a lot less risky behaviour.*"

The Partners PrEP study was conducted in east Africa with HIV-negative heterosexuals whose partner had recently

been diagnosed with HIV. Adherence was good. Study participants were very concerned about the possibility of acquiring HIV from their partner, with some feeling that this made an ongoing relationship impossible. They saw PrEP as a way they could overcome the dilemmas they faced, as described by these interviewees:

"*I feel stuck. I love my wife. I want to have sex. I don't like condoms. I don't want to get infected.*"

"*If it wasn't for this research, I wouldn't be with my wife after discovering she is HIV+. All my hopes are in this research, because I don't have any other protection. I can't say I will keep using condoms all the time.*"

However, some people taking PrEP have reported stigma from peers, who believe that PrEP will lead to increased risk-taking behaviour and may divert resources away from HIV-positive people. They have also found that some medical providers seem to be judgmental about their decision to use PrEP.

How interested are potential users in taking PrEP?

Several surveys, mostly conducted with gay men, have explained what PrEP is and asked respondents if they might be interested in taking it. Results are inconsistent but most report that over half the respondents would consider using PrEP, with greater interest among men who have risky sexual behaviour.

Barriers to the use of PrEP highlighted in a UK study included doubt about PrEP's effectiveness and concerns about its side-effects. People who think they would find adherence difficult or who do not feel at risk of HIV infection are less likely to be interested in PrEP. PrEP is highly contentious for some, especially those who speculate that other people will use condoms less if PrEP is available.

Whereas the PROUD study demonstrated demand from a sub-group of mostly well-educated gay men with strong links with gay communities, there may be other groups and populations who would benefit from PrEP but are less easily reached and may need different forms of support. Raising awareness and understanding of PrEP in a range of affected communities will be important to making PrEP available in an equitable way.

How many people are taking PrEP in the UK?

The 544 participants of the PROUD study will continue to receive PrEP until April 2016. Outside of this, current policy is that the NHS should not provide PrEP.

A few people may be buying the drugs used in PrEP from online retailers. They are not necessarily getting the HIV tests, sexual health screens, monitoring for side-effects and behavioural support that should be provided alongside the drugs. A draft position statement from the British HIV Association (BHIVA) and the British Association for Sexual Health and HIV (BASHH) gives doctors advice on how to support people in this position.

Is *Truvada* licensed for use as PrEP?

The drugs used in PrEP are already licensed for use as part of treatment for HIV-positive people. Although the European Medicines Agency has not yet licensed the drugs for use in HIV prevention, doctors are able to prescribe the drugs outside the terms of the licence. This is known as 'off-label' use and is already regularly practised for post-exposure prophylaxis (PEP).

What can we learn from the roll-out of PrEP in the USA?

PrEP has been available in the United States since 2012 but uptake was initially slow. Barriers have included lack of awareness among people at risk, concerns about side-effects, the stigmatisation of PrEP users, resistance from some medical providers, inconsistent insurance coverage and services not being geared up to provide it. During 2014 and 2015, increased advocacy and media coverage of PrEP have contributed to greater use, especially in San Francisco. In 2014, 16% of people attending the city's main sexual health clinic were taking PrEP and 60% wanted to.

So far, there is no evidence of the 'worried well' seeking out PrEP. People with riskier sexual behaviour and recent sexually transmitted infections seem to be more likely to choose to take PrEP and to have high levels of adherence.

PrEP has been controversial in the United States, with some people stigmatising PrEP users as irresponsible barebackers. Others have framed PrEP as a responsible and pro-active way to protect their health.

How long will people take PrEP for?

People are not expected to stay on PrEP forever. Experience from the United States shows that people stop taking it when they no longer feel at risk, but may go back to PrEP later. People also stop taking PrEP due to concerns about side-effects or having grown tired of the adherence and clinic visits that are required.

PrEP is best understood as being for periods of months or a few years when the risk of HIV is greatest. This could include during specific relationships, after the break-up of a relationship, at the time of sexual debut, while dealing with drug use problems, or when trying to conceive.

How much do the drugs used in PrEP cost?

Truvada is a fixed-dose combination which contains two drugs, tenofovir and emtricitabine. At present, a year's supply officially costs £4330 per person, although the NHS obtains a discount and may pay around £3000 per year.

The cost of PrEP will change substantially when the drugs are no longer protected by patent. Tenofovir will come off patent in late 2017 and emtricitabine may lose its patent protection sometime between 2017 and 2021. This means that the pharmaceutical company which originally developed the drugs will no longer have the exclusive right to manufacture them. Rival companies will be able to produce cheaper versions, which could be up to 80% less expensive.

The annual cost of healthcare, including antiretroviral drugs, for a person living with HIV is around double that of the annual cost of providing PrEP. People need to take HIV treatment for the rest of their life but PrEP will generally be needed for a much shorter period.

Is PrEP cost-effective?

Although PrEP is much more expensive than most other HIV prevention methods, studies suggest that it may be cost-effective in some circumstances. Moreover, it may sometimes be cost-saving, in other words costing less to prevent one HIV infection than the lifetime healthcare costs of that infection.

A key determinant of cost-effectiveness is selective use – PrEP is only cost-effective if it is prioritised for people at very high risk of HIV. A UK analysis found that PrEP could be cost-effective and even cost-saving if it was provided to gay men who have recently had a sexually transmitted infection or condomless sex with at least five casual partners in the past three months. However, PrEP would not be cost-effective if used by people at lower risk of HIV infection. The cost of providing PrEP to larger numbers of people would not be offset by a significant reduction in new infections.

A second determinant is the cost of the drugs used, showing the importance of using generic drugs and of pharmaceutical companies lowering their prices. The same UK analysis found that if drug prices were halved, PrEP could still be cost-effective even if it were offered to a wider range of gay men (for example, any man reporting condomless sex with a casual partner).

For the UK, there are no relevant analyses of the cost-effectiveness of PrEP in groups other than gay men.

Whether the NHS will consider PrEP to be affordable is a different question. Making PrEP widely available would be quite expensive in the short term and the financial benefits it should bring (reductions in spending on antiretroviral drugs) will not be seen for several decades.

What impact will PrEP have at a population level?

While PrEP may have significant benefits for some individuals, this doesn't necessarily mean that it will bring an end to the HIV epidemic. If demand for PrEP is low and relatively few people take it, or if health services find it difficult to identify and engage individuals at greatest risk of infection, PrEP may only make a small dent in the number of new infections. If the availability of PrEP leads to fewer people using condoms, then this could offset the benefits of PrEP. If uptake is overly concentrated in some demographic groups, it may deepen health inequalities.

How should provision of PrEP be targeted in the UK?

PrEP policies should be based on the specifics of local epidemiology so that PrEP reaches individuals who are most likely to benefit from it – those who are at elevated risk of acquiring HIV and are also able to achieve good adherence.

For gay men, several studies have identified behaviours strongly associated with acquiring HIV, and these can be used to guide PrEP policies. Less is known about adherence, but in some studies it has been better in individuals at greater risk of HIV. PrEP could be offered to men recently diagnosed with a sexually transmitted infection, or reporting receptive anal intercourse without a condom, or higher partner numbers. Other factors, such as recent use of post-exposure prophylaxis (PEP) or chemsex (sexualised drug use) might also be relevant.

While individuals who have HIV-positive sexual partners might appear to be ideal candidates for PrEP, they may have a relatively low risk of infection if their partner is on treatment and has an undetectable viral load. But people's relationships can change rapidly – methods for identifying individuals who could benefit from PrEP need to focus on current factors and be sensitive to the way in which people go in and out of risky behaviour.

Based on studies with heterosexual couples of different HIV statuses in African countries, researchers developed a risk assessment tool to identify the HIV-negative partners at greatest risk of acquiring HIV. This takes into account younger age, a high viral load, having sex without a condom, living together, not having children and circumcision status (if the man is HIV-negative).

As our understanding of the behaviours associated with HIV acquisition in heterosexual adults in the UK is less well developed, it may be challenging to define criteria for PrEP provision for heterosexuals. Decisions may need to be made on a case-by-case basis.

A draft position statement from BASHH and BHIVA states: "BASHH and BHIVA strongly recommend that PrEP be made available within a comprehensive HIV prevention package to MSM who are engaging in condomless anal sex, and to HIV negative partners who are in serodiscordant heterosexual and same sex relationships with a HIV positive partner whose viral replication is not suppressed."

What do international guidelines say about PrEP?

The World Health Organization recommends that in all countries, PrEP should be available to men who have sex with men, alongside other HIV prevention interventions. It may also be provided to people who have an HIV-positive partner. In the United States, the Centers for Disease Control and Prevention (CDC) recommends PrEP for the same groups, as well as people who inject drugs and heterosexual adults "who are at substantial risk of HIV acquisition". The European Centre for Disease Prevention and Control (ECDC) advises European countries to consider "integrating PrEP into their existing HIV prevention package for those most at-risk of HIV infection, starting with MSM".

What other services need to be provided alongside the drugs?

People thinking about using PrEP need to be given enough information about PrEP and other prevention options to help them decide whether PrEP is appropriate for them.

The initial assessment before a person begins PrEP needs to include the individual's risk of HIV infection; tests for HIV, sexually transmitted infections, pregnancy, hepatitis B and kidney function; and evaluation of any medical problems that could be seroconversion symptoms. People beginning PrEP may benefit from advice on developing routines of pill taking.

When taking PrEP, regular HIV testing (to prevent the development of drug resistance) and regular monitoring for side-effects (especially kidney problems) are essential. These visits also provide an opportunity to screen for sexually transmitted infections, engage patients with discussions around sexual risks, offer other behavioural interventions, and make condoms available.

The CDC's guidelines include detailed recommendations on how to provide PrEP.

Where will PrEP services be provided?

In the UK, sexual health (GUM) clinics are the obvious location as many people who would benefit from PrEP already attend them and many staff are skilled in discussing risk behaviours. Providing PrEP requires experience of prescribing antiretrovirals, which many sexual health clinicians have. Partnerships with community organisations may help raise awareness of PrEP in the wider community.

Who will pay for NHS provision of PrEP and how will decisions be made?

In England, the cost of the drugs used as PrEP would be borne by NHS England, whose specialised services team is responsible for all commissioning of antiretroviral drugs. Staff and facility costs would need to come from local authorities, who commission sexual health services. Joint commissioning will therefore be needed.

Within NHS England, its Clinical Reference Group for HIV includes HIV clinicians, commissioners and patient representatives. They are currently preparing a *draft* policy on whether PrEP should be provided and to whom. This will then be evaluated by other groups within NHS England, in terms of its clinical efficacy, safety, cost effectiveness and affordability. This comes at a time when there is pressure on NHS England to reduce its overall spending on specialised services, which includes cancer and hepatitis C treatment.

In Scotland, Wales and Northern Ireland, NHS services are commissioned and organised differently. It is unclear who will make decisions about providing PrEP or when they will do so.

Clinical guidelines prepared by groups such as the British HIV Association (BHIVA) or the British Association for Sexual Health and HIV (BASHH) can make recommendations to doctors on the most appropriate use of PrEP. They can influence clinical practice, but would not oblige commissioners to pay for PrEP.

Could other drugs and delivery methods be used as PrEP?

So far most studies have examined the use of *Truvada* (tenofovir and emtricitabine) pills as PrEP. But PrEP using a single-drug regime of tenofovir could be possible and would be cheaper. One study found that it was only a little less effective than *Truvada*, with the difference not being statistically significant. The use of maraviroc and other antiretroviral drugs is being investigated.

Moreover, PrEP does not necessarily need to involve daily pills. Vaginal microbicide gels are also a form of PrEP, but adherence to these has been poor for a range of complex reasons.

It may also be possible to provide antiretrovirals through a vaginal ring which only needs to be replaced every month – this technology is already used for contraceptives and a single ring could potentially combine HIV prevention and contraception. Similarly, long-acting injections are also being investigated – these may provide protection for up to three months at a time.

Key points

- Pre-exposure prophylaxis (PrEP) involves HIV-negative people taking antiretroviral drugs to lower their risk of HIV infection. Several studies have shown it to be effective as long as the drugs are taken regularly.
- Concerns about potential problems with side-effects, drug resistance and sexual behaviour change have not been borne out. PrEP users say it provides an 'extra layer of protection' and 'peace of mind'.
- While PrEP has been most often studied as a daily pill, alternative dosing schedules (before and after sex) and alternative products (vaginal rings, injections, etc.) may be possible.
- Although PrEP is more expensive than other HIV prevention methods, it is likely to be cost-effective as long as provision is prioritised for individuals at increased risk of HIV infection.
- Until an NHS policy on PrEP is decided, the only people able to access PrEP in the UK are the 544 gay men taking part in the PROUD study. It's unclear whether PrEP will be made available to heterosexuals.

Further reading

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