



Pre-exposure prophylaxis to prevent HIV among MSM in the UK

The need for new prevention approaches

Nationally, one in every 17 MSM aged between 15 and 59 is living with HIV, and in London it is one in eight. There were 3,250 new HIV diagnoses in MSM in the UK in 2013, of which 2,470 were acquired in the UK. HIV incidence seems to be increasing among MSM in the UK despite expanded HIV testing services, widespread treatment of positive individuals, behaviour change interventions and provision of post-exposure prophylaxis (PEP). When used correctly and consistently condoms are a highly effective way to prevent HIV and other sexually transmitted infections. However, with HIV infections remaining high it is clear that condoms are not a sufficient option for all men. Additional HIV prevention options are urgently needed for individuals at high risk of infection (who cannot or do not always use condoms) to protect themselves, and in doing so, protect their sexual partners.

Pre-exposure prophylaxis (PrEP)

Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy that involves HIV-negative individuals taking antiretroviral drugs (drugs usually used to treat HIV) to reduce their risk of becoming infected if they are exposed to the virus. The most commonly used pill for PrEP is Truvada, which combines two antiretroviral drugs.

The efficacy of Pre-exposure Prophylaxis in trial conditions

Previous placebo controlled trials of PrEP have shown efficacy ranging between 44% to 73%, although two trials among women in Africa showed no effect at all. The variations are due to differences in adherence. In placebo controlled trials, participants do not know whether they are taking the active drug, or a placebo (dummy) drug. This may lead to poor adherence, as if they believe they are likely to be on the placebo, they will not anticipate getting any benefit from taking it regularly.

On the basis of this evidence, daily Truvada was approved for HIV PrEP use in the USA in 2012, to be offered as part of a comprehensive risk reduction package usually provided by private health care schemes.

More recently, the IPERGAY study announced their results. IPERGAY was a placebo-controlled trial in France and Canada, looking at the efficacy of PrEP taken before and after sex (where two Truvada pills are taken between two to 24 hours before anticipated condomless sex, and then, if sex happened, two separate one-pill doses in the two days following sex) rather than daily dosing. IPERGAY found that PrEP was highly efficacious at preventing HIV. The only HIV infections seen were in the placebo group, or in individuals who had stopped taking their drug.

However, there were a number of important questions that needed to be addressed before clinicians

Key points

- There is an urgent need for additional HIV prevention tools, with approximately 2600 MSM being newly infected with HIV each year for the last decade.
- The PROUD study was conducted in England and showed the PrEP was highly effective at preventing HIV infection among MSM in a 'real life' healthcare setting
- Taken properly, PrEP can prevent HIV infection, but it will not prevent the other sexually transmitted infections. This is why it is important to continue to promote condom use.
- HIV incidence in the population who came forward to access PrEP was much higher than we expected, based on sexual health clinic data, showing the offer of PrEP brings forward people at high risk of HIV.
- In the PROUD study PrEP use did not increase sexually transmitted infections, even though there was some evidence of a larger proportion of PrEP recipients at one year who reported receptive anal sex with 10 or more partners without a condom
- The sexual health clinics that took part in the PROUD study were able to integrate PrEP into their routine HIV and STI risk reduction package.

and policymakers could decide if PrEP would be a feasible and cost-effective approach to tackling the HIV epidemic in the UK:

- If people know they are receiving an active drug that prevents HIV, will their risk behaviour change, offsetting the benefit of PrEP and leading to an increase in other sexually transmitted infections (STIs)?
- To whom should PrEP be offered?
- Under what conditions would PrEP be cost-effective in the UK?
- Do gay and other MSM in the UK want access to PrEP?
- Will they adhere to PrEP well enough to get prevention benefits?
- Can sexual health clinics integrate PrEP into routine practice?

PROUD

In the PROUD study 544 gay and other MSM were randomised to either receive PrEP immediately (the immediate group), or after 12 months (the deferred group). All participants were tested for HIV and other STIs approximately quarterly. This allowed researchers to compare rates of HIV and STIs between the people who were on PrEP (in the immediate group) and those who were not (in the deferred group). Participants were also offered the standard HIV and STI prevention services provided at their clinic.

Who took part in PROUD?

The median age of PROUD participants was 35. Typically, participants were:

- white (78%)
- educated at university level (61%)
- in full-time employment (72%)
- born in the UK (60%)

The eligibility criteria for PROUD were broad, allowing inclusion of participants who reported at least one anal sex act without a condom in the preceding 90 days. In theory, this would mean that half of MSM

attending sexual health clinics would fit this criteria. But the incidence rate in the deferred group of PROUD was approximately seven times the national estimate for MSM attending sexual health clinics. This implies that despite the broad eligibility, the PROUD study population was highly self-selected; people at high risk volunteered to take part. Many PROUD participants had baseline characteristics which put them at particularly high risk of HIV:

- One in three had been diagnosed with rectal gonorrhoea or chlamydia in the preceding 12 months
- One in three had used post-exposure prophylaxis in the prior 12 months
- The median number of reported sexual partners in the 90 days prior to enrolment was 10, of whom a average of two were without a condom where the participant was insertive (top) and two were without a condom where the participant was receptive (bottom).
- More than four in 10 participants reported recently using one or more of the drugs that increase sexual disinhibition (such as crystal meth, G or mephedrone)

This suggests that the offer of PrEP generally attracts those men who are most likely to benefit from it. This is a highly encouraging finding for PrEP implementation in the UK.

The 'real world' effectiveness of PrEP in the UK

Although the PROUD pilot study was not expected to be large enough to measure the effectiveness of PrEP, in October 2014 the Independent Data Monitoring Committee recommended that men on the deferred group who had not yet started PrEP should be offered it immediately. This is because there was sufficient evidence to show that PrEP was highly effective; the HIV incidence was substantially lower in the immediate PrEP group than in the deferred group.

Of the 544 participants who joined the study, 275 were allocated to receive PrEP immediately and 269 after 12 months. In the deferred group 20 men were newly infected with HIV during the deferred period. This equates to nine infections per 100 person-years. This was much higher than we expected based on the incidence seen in sexual health clinics, which was 1.2 infections per 100 person-years in 2012. This high incidence was despite the fact that a third of participants in the deferred group used post-exposure prophylaxis at some time during the deferred period.

In the immediate PrEP group three men were newly infected with HIV during their first year in the study. This equates to one infection per 100 person-years. One of these men is thought to have been infected just before starting the trial, so tested negative at enrolment but positive within four weeks. The other two participants had not collected their Truvada prescriptions for several months, and were unlikely to have been using PrEP at the time they were infected.

Taking account of this imperfect usage, PrEP reduced HIV infections by 86%, preventing eight new infections per 100 person-years. This is a higher level of protection than that observed by previous trials (although identical to the level of protection observed in the IPERGAY trial). With this high level of protection, you would need to give PrEP to only 13 people like those in the PROUD study for a year to directly prevent a new HIV infection.

Adherence is hard to measure, as people may be reluctant to admit to not taking their tablets as instructed. Data on self-reported adherence in PROUD were not completed consistently enough to provide a reliable estimate of adherence over time. However, we know that adherence was high based on the high level of effectiveness observed in the study and the number of prescriptions of PrEP collected. Enough Truvada was prescribed to participants in the immediate group to allow them to have used

PrEP for 88% of the follow-up time. The most reliable way to tell if someone has taken their tablet is to carry out a blood test to see if the drug can be detected in the blood. In 52 participants who reported taking drug and had plasma samples tested, the drug was detectable in all samples.

Truvada was shown to be safe and well-tolerated in the PROUD study. This is consistent with previous studies. Side effects were infrequent, mild and transient. A small number of individuals required more frequent renal monitoring than annually; these were older participants with co-morbidities on other medications. While some viral resistance was seen in PROUD participants who acquired HIV, the mutations did not preclude effective treatment.

The sexual health clinics that took part in the PROUD study were able to integrate PrEP into their routine HIV and STI risk reduction package. The trial was pragmatic, seeking to show whether PrEP could be easily integrated into routine practice, so there were no screening visits before starting PrEP, and, unlike other PrEP trials, participants did not receive intensive adherence support. All this indicates that a PrEP programme could feasibly be rolled out in UK sexual health clinics.

Did PrEP lead to changes in risk behaviour?

Based on self-reported sexual behaviour, there was no significant difference for either group between the number of anal sex partners at baseline and 12 months. However, there was some evidence of a larger proportion of PrEP recipients at one year who reported receptive anal sex with 10 or more partners without a condom. But the self-reported data on sexual behaviour in PROUD is limited by poor levels of completion of the sexual behaviour questionnaires and diaries. Because of this, the data on STIs is the most reliable indicator we have of whether PrEP changed sexual risk behaviour. Participants in PROUD were at a high risk of bacterial STIs, both before and during the study. More than

half of participants were diagnosed with a bacterial STI during the study. Despite this, there was no significant difference in any rectal STIs (the most specific marker of receptive anal sex without a condom) between the immediate and deferred groups.

These data from PROUD add substantially to our understanding of how PrEP is likely to affect risk behaviour. Participants in the immediate PrEP group knew they were on a drug that previous trials had shown prevents HIV. The rectal STI data indicates that this knowledge did not cause them to adopt substantially riskier behaviour. Previous trials have been unable to assess this, as the use of a placebo meant participants were unable to be sure if they were protected from HIV or not.

Is PrEP cost-effective in the UK?

Based on data from the PROUD study, two cost-effectiveness models of PrEP for MSM in the UK are being developed to see under what conditions PrEP would be cost effective, and what effect it could have on the UK HIV epidemic.

The preliminary results of the modelling, along with previous studies looking at the cost-effectiveness of PrEP, indicate that the main drivers of whether or not it is cost effective are HIV incidence and drug prices. If PrEP was targeted at those at highest risk of HIV (similar to those who took part in the PROUD trial), or the price of Truvada falls below 50% of the current full list price, PrEP is likely to be cost-effective (or even cost-saving) in the UK. More details of this will be available when the results of these modelling studies are published.

Adopting a 'before and after sex' approach to PrEP (as used in the IPERGAY study) rather than daily dosing could cut the amount of Truvada required (and therefore drug cost) by approximately 50%, increasing the cost-effectiveness of PrEP.

Demand for PrEP

The potential impact of PrEP on the UK HIV epidemic depends on the level of demand amongst those in need of it. The PROUD study was not designed to measure the level of demand, although we were able to show that there was interest in PrEP among some MSM, and people who presented themselves for PrEP were at sufficiently high risk of HIV to benefit from PrEP. While PrEP will not be the HIV prevention method of choice for many MSM (eg. those who consistently use condoms), the results of PROUD have been enthusiastically received by community groups and participants. Groups such as NAT and the Terrence Higgins Trust have called for the NHS to make PrEP available to all who need it as soon as possible.

As part of the PROUD study we are conducting in-depth one-to-one interviews with approximately 50 participants. Once analysed, these data will provide a rich understanding of how people incorporate PrEP into their everyday lives. Participants who have spoken publicly about the PROUD results have highlighted how PrEP has given them new hope that they can avoid HIV and reduced the fear, anxiety and guilt that surrounds sex for many. Participants view PrEP as a tool to help prevent HIV during periods in people's lives when they may take more risks than at other times in their lives – and this is helping people reimagine their futures without feeling that HIV is inevitable.

Conclusions

The number of new HIV infections among MSM has not decreased over the last decade. This, along with the high HIV incidence in the deferred group of PROUD, emphasises the need for PrEP in addition to current HIV prevention approaches. PrEP is highly effective at preventing HIV among MSM in the UK, in 'real world' conditions. Use of PrEP does not appear to increase the risk of other STIs. Modelling work shows that PrEP can be cost-effective or even cost-saving for the NHS, depending on who is offered it, and drug prices.

Next steps

The NHS England HIV Clinical Reference Group has appointed a sub-group to prepare the documentation for the Clinical Priorities Advisory Group to review. The review will include evaluation of clinical effectiveness, safety, cost effectiveness and affordability.

In England, the cost of the drugs used as PrEP (if commissioned) would be borne by NHS England, whose are 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.

In Scotland, Wales and Northern Ireland, NHS services are commissioned and organised differently.

Recommendations

BHIVA and BASHH have reviewed the evidence and updated their position statement on PrEP, following the release of the PROUD and IPERGAY results. Their recommendations may influence clinical practice, but do not oblige commissioners to pay for it. They 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.
- Healthcare workers should note that PrEP is one of several prevention tools and discuss the options available with their service users.

The PROUD researchers make the following additional recommendations:

- There are likely to be sub-populations within other risk groups (heterosexuals and injecting drug users) who would benefit from PrEP. We need research into how best to identify these individuals.
- It may be that the offer of PrEP within research projects will help to identify these sub-populations, so this research should be strongly encouraged.
- Advocates that represent these groups should direct their efforts into lobbying for funding for this research to collect the necessary evidence.

Further information

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- Responses to the PROUD results http://www.proud.mrc.ac.uk/pdf/Responses%20to%20the%20PROUD%20results_24Feb2015.pdf

Contacts

For more information on the PROUD study, please email mrcctu.trial-proud@ucl.ac.uk or visit http://www.ctu.mrc.ac.uk/our_research/research_areas/hiv/studies/proud/

Credits

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