

Uptake of PrEP for HIV slow among MSM

Prescriptions of the pill for HIV pre-exposure prophylaxis have been slow in the USA. But trials of the therapy are gathering pace worldwide. Tony Kirby and Michelle Thornber-Dunwell report.

In July, 2012, the US Food and Drug Administration approved a combination pill of tenofovir and emtricitabine (marketed as Truvada, Gilead Sciences, USA) for pre-exposure prophylaxis (PrEP) for HIV. The once-daily drug was approved to reduce the risk of sexually acquired HIV infection in high-risk, seronegative individuals. However, uptake of the pill as PrEP in the country—the only nation in the world to license the drug for this indication—has so far been slow.

One of the most comprehensive analyses of prescriptions for PrEP produced some surprising findings. The research, presented at last year's Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting in Denver, Colorado, USA, found that 1774 people had used the tenofovir and emtricitabine pill as PrEP (off-label and post-approval) between January, 2011, and March, 2013. Of these, 48% were women, and the users were widely spread across the USA. However, despite this slow start, there are signs that the rate of prescription is increasing, with 350 issued in the first 3 months of 2013 alone.

Kenneth Mayer, professor of Medicine at Harvard University and the medical research director at Fenway Health, a community centre in Boston, MA, USA, believes that as with other innovations, uptake of PrEP will be slow until knowledge of past and ongoing trials become widely known in both the MSM community and the general population. Mayer also points out that there are many more MSM actually using PrEP, but currently this is within clinical trials. Thus prescriptions could rise substantially once the current crop of clinical studies in the USA comes to an end.

Communication challenge

"One of the largest challenges PrEP faces is that experts have said for three decades now that condoms are the most effective way to prevent HIV infection", says Mayer. "Many of these same doctors and also charities and advocacy groups are very uncomfortable about anything that changes that message."

"...PrEP will only be truly effective as part of a comprehensive sexual health package, since it offers no protection for other sexually transmitted infections (STIs) or hepatitis C."

Mayer says that Gilead Sciences may have been reluctant to market the drug so far for exactly these reasons, but has been happy to fund research to establish PrEP's effectiveness and thus its potential market. "Even for PrEP's biggest supporters, issues like cost-effectiveness, toxicity, and non-adherence are all issues that must be faced if this intervention is to become available on a large scale", says Mayer.

He adds that most MSM who want PrEP will visit their family doctor, leading to awkward conversations about admissions of unprotected sex during consultations. "Both MSM and doctors have to overcome this stigma and discomfort if PrEP is to fully realise its potential", says Mayer, who adds that PrEP will only be truly effective as part of a comprehensive sexual health package, since it offers no protection for other sexually transmitted infections (STIs) or hepatitis C.

New studies

A key factor in convincing policy makers to consider PrEP for HIV

prevention could be whether less frequent than daily dosing could give sufficient protection against HIV—a question that will likely be answered by two ongoing trials, one by the US National Institutes of Health in New York City, Bangkok, and Cape Town (Project Adapt; HPTN 067), and the second by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS)—the IperGay study—a placebo-controlled trial. "We already have animal data that suggests less-than-daily dosing could be enough to provide protection, but this must be backed up by human studies", says Mayer. Fenway Health, as well as doing research sponsored by Gilead, is also studying maraviroc (marketed as Selzentry, Pfizer, USA) for PrEP as part of the multi-site, NIH-funded HIV Prevention Trials Network. Mayer says that this drug has a more favourable side-effect profile than tenofovir, and is also less frequently used in care of HIV-positive patients than tenofovir, thus reducing risk of drug resistance developing. This study will probably report initial findings in 2015, but efficacy trials will take longer.

In Australia, three separate studies have begun (in New South Wales,



MSM might be reluctant to talk to their family doctor about PrEP, say experts



Dr P Marazzi/Science Photo Library

Victoria, and Queensland). As well as high-risk MSM, the studies will include HIV-negative people (both homosexual and heterosexual) who are in relationships with HIV-positive partners, including couples who are trying to conceive. "We are also enrolling people who are eligible for PrEP but who don't want to take it wherein they would consent to do a single online interview at baseline about why they don't want to use PrEP, and also consent to us following up their sexual behaviour, condom use, and STI and HIV testing patterns and results", says Edwina Wright, chief investigator of the VICPrEP study and associate professor in infectious diseases, Alfred Hospital/Monash University and Burnet Institute, Melbourne, VIC, Australia. Other PrEP trials have begun in both high-income countries and Africa, including those of anal and vaginal gels, vaginal rings, and injectable drugs.

In the UK, the PROUD study pilot is currently recruiting patients at 13 clinics in England. It is designed to assess the effectiveness of PrEP in preventing HIV-infection in high-risk, HIV-negative MSM. The pilot has recently recruited its 400th participant, with a target of 500. One half of the participants will be randomised to receive daily PrEP immediately, while the other half will receive daily PrEP after 12 months. Should the study show that PrEP

prevents HIV infections at any point, PROUD's independent committees can recommend the delayed PrEP arm also receive the drugs immediately. Should no difference be found, it will be clear that a larger trial is needed that will be better powered to show any potential difference.

"A range of high-risk men have volunteered for the study, all of whom have had at least one, but usually more, unprotected anal sex encounters in the past 3 months, and will likely continue that high-risk behaviour", says PROUD chief investigator Sheena McCormack from the Medical Research Council Clinical Trials Unit at University

"People are also worried that MSM that were previously low risk could drift into a higher risk category with PrEP..."

College London, UK, where she is also a professor of clinical epidemiology. "The study includes MSM that are usually the receptive partner in anal sex acts, those that are usually insertive, and those who regularly exhibit both behaviours."

Despite concerns that some MSM may drop out of the study once finding out they were in the "delayed" PrEP arm, McCormack says that there have only been rare examples of this, with most participants accepting they will eventually receive the medication. "While we are seeing the delayed-PrEP arm being less likely to come to all follow-up appointments, there have been very few participants lost to follow-up so far", says McCormack.

Risky behaviour

One of the major concerns of HIV experts, health providers, and advocacy organisations is that the advent of PrEP could see risk compensation behaviour increase, with MSM at high risk reducing condom use, despite the risk of

other sexual transmitted infections, including hepatitis C. "People are also worried that MSM who were previously low risk could drift into a higher risk category with PrEP", says McCormack. "The PROUD trial plans to address exactly this issue, characterising whether behaviour in the first 12 months of follow-up differs between those with and without PrEP, and provide vital answers for policy makers and HIV experts on risk compensation. For example, if it's found that those receiving PrEP immediately have higher rates of STIs than the delayed PrEP group, it will be suggested that this riskier behaviour is specifically due to PrEP. It's crucial to have these answers and work out whether PrEP on a large scale will be cost effective."

Additional method

Until such time as trials worldwide provide definitive answers, HIV charities and advocacy organisations in the UK, including the National Aids Trust and the Terrence Higgins Trust, have come together to publish a joint statement on PrEP, making clear that "PrEP is not a replacement for condom use. Instead it is an additional method of preventing HIV transmission, to be added to the other strategies that gay men already use." It also echoes the uncertainty expressed by McCormack about whether or not PrEP could encourage increased risky behaviour. But should trials prove successful and PrEP come into widespread use, McCormack hopes that educated MSM in high-income countries will be its greatest advocates, encouraging those people for whom it could be effective to consider using it. "Here in the UK, we also need to consider how best to reach black African heterosexual men and women, who have among the highest HIV rates but tend to be less frequent users of sexual health clinics and services."

Tony Kirby, Michelle Thornber-Dunwell