



PrEP is a key HIV prevention strategy, but how do we chart its success?

By Clovis Palmer

What is PrEP?

Despite tremendous efforts to address HIV worldwide, the rate of new infections remains unacceptably high, demonstrating an urgent need for new prevention strategies. HIV pre-exposure prophylaxis (PrEP) is a new approach that involves the use of antiretroviral drugs by HIV-negative individuals to reduce the risk of acquiring HIV. The daily use of a combination of drugs: tenofovir/emtricitabine (Truvada) as oral PrEP has been shown to be effective in several clinical trials. The convincing data from these studies have prompted the Centers for Disease Control and Prevention in the USA, and the World Health Organization (WHO), to develop and release guidelines recommending the use of oral PrEP for high-risk populations.^{1,2}

While the scale-up of PrEP is well under way in many cities in the USA, several implementation questions remain unanswered regarding how PrEP will reach high risk populations within that country and around the globe. Concerns have been raised regarding cost effectiveness, ethical issues, and the possible explosion of other sexually

transmissible infections (STIs). Some critics have also pointed to the risk of emergence of resistant HIV strains and adverse side effects.^{3,4}

Some argue that PrEP complicates and distracts from the efforts required to design and find an effective HIV vaccine.⁵ Others question the public health impact of PrEP scale-up in the real world due to slow uptake, risk compensation⁶, poor personal adherence^{7,8,9} and, in the context of Australia, the cost effectiveness beyond HIV-negative men who have sex with men (MSM) in a discordant relationship¹⁰.

Internationally, these issues have been the subject of at times acrimonious debates. While the research unequivocally shows that PrEP works in a clinical setting, there are those who sharply oppose it, or cannot see past limitations that could be used as a roadmap to improve its implementation in the real world.

The supporters and the critics

Personally, I don't think PrEP should be debated in the context of 'for or against'. I find it difficult to comprehend why someone would deny any individual

the choice of accessing an HIV prevention method that's been proven to be safe and effective.

Official recommendations support offering PrEP to people at greatest risk of HIV acquisition, but maximising the public health impact of PrEP may require a broader approach – with guidelines akin to those already recommended for people living with HIV.

PrEP Guidelines

According to current US Food and Drug Administration (FDA) guidelines, PrEP protocol should include:

- 1) baseline HIV test
- 2) adherence to daily use
- 3) periodic (every three months) HIV/STI check-up
- 4) monitoring of kidney and liver functions
- 5) use of condoms.

These PrEP support guidelines generally fall into community-based, monitoring, technology, and integrated sexual health promotion approaches. Formalising these approaches beyond PrEP trials toward a more comprehensive roll-out

protocol, in often socio-economically-deprived environments (some where the local language differs from the national language), will be no easy feat.

Interpreting the efficacy of PrEP

Several randomised clinical trials demonstrated that daily use of tenofovir alone, or in combination with emtricitabine, can reduce the risk of HIV transmission in heterosexual serodiscordant couples, men who have sex with men, transgender women who have sex with men, and sexually active heterosexuals.^{11,12,13,14} In these trials, the overall reduction in HIV risk provided by oral PrEP ranged from 0%–75%. The iPrEX study, the first of these studies, provided results that demonstrated an overall risk reduction of 44% in 2,499 enrolled MSM and transgender women from Latin and North America, Asia and Africa.¹⁵

iPrEX provided the first proof of principle that antiretroviral therapy (ART) is an effective HIV prevention tool. The study also underscored the significance of adherence, providing a 92% risk reduction in those who adhered more consistently to daily pill-taking.¹⁶ Despite the wide range in efficacy estimates in the different trials, the general consensus is that adherence is the single most important factor determining the success of PrEP.

Indeed, studies such as FEM-PrEP¹⁷ and VOICE¹⁸, which were among women only, showed that those who had suboptimal amount of drugs in their blood were not protected from HIV – reinforcing the significance of adherence. This begs the question: how do we calculate an intervention's success? Shouldn't the effectiveness of an intervention also be judged based on its availability and its ease of adherence? Interpretation of the data becomes even more complex when one takes into account the use of condoms by participants in these studies.

Initial concerns that PrEP may not work for women were addressed by other studies; TDF2¹⁹ and Partners PrEP²⁰ demonstrated a 78–86% effectiveness. However, it does appear that factors other than adherence, such as differential drug penetration in the female genital tract, may partially contribute to a less forgiving nature of PrEP in women who miss doses – the drug being at higher levels in the rectum than in the female genital tract.

Evidence of safety and reduced HIV risk at the individual level has positioned PrEP as an important component of a comprehensive approach to HIV prevention. However, modelling studies suggest that the public health impact of PrEP could be limited by slow uptake, poor adherence, and increases in risk behaviour (risk compensation).²¹ In Australia, the only country remotely on track to attain the ambitious UNAIDS target of '90-90-90' by 2020 (90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will be on sustained ART, 90% of all people on ART will have below detectable viral load), PrEP could potentially end HIV transmission in high risk populations. But when we consider this in the wider context of the Asia and the Pacific, the challenges are magnified, and our goal becomes elusive.

How to overcome the limitations of PrEP?

Potential side effects

Oral PrEP appears to be generally safe and well tolerated, but has been associated with small yet statistically significant decreases in liver and kidney function and bone mineral density (BMD). These side effects tend to resolve after discontinuation of PrEP. However, the long-term clinical significance of these changes remains unclear, and effects on users with underlying health conditions, and elevated risks of bone, liver and kidney diseases, are unknown. What is evident is the importance of baseline assessment and ongoing monitoring of HIV status, BMD, renal and liver function, and pregnancy.

Promisingly, one clinical trial is trying to shed light on the potential utility of vitamin D supplementation for individuals who use PrEP (CCTG595VitD).²² This is a good example of where early

observations can be used as a roadmap to improve intervention.

Development of resistant strains

Development of drug resistance is a concern for individuals who use PrEP after unknowingly acquiring HIV, because PrEP may not fully suppress the virus. Fortunately, drug resistance has been rare among PrEP users who were HIV-negative at enrolment.^{23,24,25} One approach to allay the fears of HIV drug resistance is to increase accessibility to testing technologies with shorter window periods, such as nucleic acid amplification tests and antigen/antibody combination tests, to discount acute HIV infection prior to PrEP initiation. Another approach is to develop creative strategies to improve adherence.

Ethical issues regarding availability

The global public health impact of PrEP is not only dependent on how many people use it, but also on who uses it. Thus, prioritising PrEP uptake among those at highest risk is important to maximise its overall impact and cost-effectiveness. At the pinnacle of the risk spectrum are economically marginalised groups in resource-rich and resource-constrained countries, for whom PrEP is not a current option due to economic and structural barriers.

Many critics have cited the demographic of the participants in the iPrEX study: 55%, 15% and 12% from Peru, Brazil and Ecuador, respectively. They question the ethical undertones pertaining to the lack of availability of PrEP for those volunteers or other at-risk populations in these countries. However, it would seem unethical to deny someone the benefits of PrEP. If a woman has a family history of breast cancer, should she be denied the BRAC1/2 genetic test simply because it is unavailable to someone else?

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Cost-effectiveness

Treatment as prevention, in which an HIV-infected partner with undetectable viral load is in a serodiscordant relationship, is already associated with a 96% reduction in transmission risk²⁶, which raises the question whether PrEP has limited incremental value in these scenarios. In a recent economic evaluation of the cost-effectiveness of 'on demand' HIV PrEP for men who have sex with men in Canada, considering direct antiretroviral and psychosocial costs along with outpatient, inpatient and emergency department costs, the cost effectiveness ranged from cost-saving to largely cost-effective.²⁷ But can we truly put a monetary value on averting the experience of stigma that people living with HIV are routinely exposed to? Not to mention the non-negotiable lifelong burden of adhering to daily HIV medication and the impact of laws in many countries that force people with HIV to disclose?

Barriers

Among individuals who have an interest in PrEP, the lack of access to a health care provider who is knowledgeable or comfortable in talking about PrEP may present a significant obstacle. The high cost of PrEP is indisputably a major barrier to uptake globally, particularly in resource-rich countries where only branded Truvada is currently available. In the US, PrEP can be accessed by private health insurance, and Gilead has implemented a financial assistance program for those without insurance. The extent of financial coverage in other countries is unresearched.

Emphasis should also be placed on increasing physician comfort and

confidence in prescribing PrEP. An increased capacity to deliver PrEP could involve galvanising other health care providers such as nurses and pharmacists in prescribing and monitoring PrEP.

Education regarding HIV infection risk and safety concerns will continue to form the fundamental basis of PrEP, highlighted by the iPrEX OLE²⁸ and US Demonstration Project²⁹ where low perceived risk of HIV infection, safety concerns, and pill burden, emerged as potential barriers for PrEP use. Negative and judgemental reaction towards PrEP users, referring to them as 'Truvada Whores', has characterised negative media portrayal of PrEP in the US; however, PrEP advocates and users have reclaimed this phrase, proudly wearing 'Truvada Whore' t-shirts in response.

The future of PrEP: what might it look like?

Naturally, one of the main limitations of PrEP is the same that exists for millions of people living with HIV: pill fatigue. Studies such as the Ipergaly trial, evaluating on-demand PrEP with Truvada, have demonstrated an efficacy rate of 96% with four doses per week, suggesting intermittent strategies may be a viable option to pacify the fears of pill fatigue and affordability.³⁰

We are likely to see the addition of more convenient formulations including the promising long-acting injectable drugs currently in clinical trials – such as rilpivirine LA (administered monthly), and cabotegravir (administered quarterly), slow-release dapivirine intravaginal rings, gels and more ambitious developments such as subdermal implants and patches, which may limit systemic drug exposure

and potential toxicities. It is not too preposterous to imagine a chewable PrEP – perhaps combined with vitamin D/calcium to improve convenience in situations where potable water might be out of arm's reach.

Participants in some studies have expressed interest in incorporating drug-level testing, with results guiding adherence counselling. Integrating technology with many of these strategies has the potential to bring down costs, decrease side effects, reduce pill fatigue and facilitate adherence. Maximising the public health impact of PrEP will require roll-out to be combined with innovative interventions to promote uptake, support adherence and prevent increases in risk behaviour.

PrEP will also be seen for having benefits that go far beyond its direct effect on HIV risk. It will provide an opportunity to engage high-risk individuals with health services that they otherwise may not access. This includes services that are an integral part of the normal PrEP package, such as regular HIV/STI testing, medical check-ups and risk-reduction services.

What is happening in PrEP research?

Several studies underway are giving us a forecast into the future, including evaluating text message-based adherence interventions, and diversification of demographics to include female and transgender sex workers (PrEP-India, NCT02148094³¹), young heterosexual men and women (CHAMPS, South Africa NCT02213328³²), young MSM of colour (CRUSH, USA NCT02183909³³), and MSM and heterosexual men and women (VicPrEP³⁴ and PrELUDE, NCT02206555, Australia³⁵). We should take advantage of technological advancement and social media and text messaging to increase awareness about PrEP.

Leaving no-one behind

By contextualising research findings and novel technologies to bridge the gap between science and the community, we can endeavour to implement PrEP on a global scale in regions where culture and infrastructure create an environment for practical PrEP roll-out. The work ahead is challenging if optimal access

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to PrEP is to be achieved in resource-constrained countries in Eastern Europe, Asia, Central and Latin America, and the Caribbean, where PrEP trials are absent or minimal. Vital to this will be the plasticity of local governments, where policies will need to be instigated to support successful implementation of this promising HIV prevention strategy. This will ensure that no-one is left behind.

How can I access PrEP if I am interested?

Truvada is not yet been approved for use as PrEP in Australia; however, most STI clinics have healthcare professionals who are experienced in caring for people with HIV and should be receptive to enquiries about PrEP. Familiarising yourself with credible PrEP-related information and consulting a healthcare provider to discuss your options is important, so that you can make informed choices.

Links to resources and information about current options for accessing PrEP in Australia are available from the Australian Federation of AIDS Organisations (AFAO) website at: <https://www.afa.org.au/about-hiv/hiv-prevention/pre-exposure-prophylaxis-prep>

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