Pre-exposure Prophylaxis (PrEP)

ACON believes that gay men and other homosexually active men (GHAM) should have access to the full range of proven prevention technologies in order to reduce HIV transmission and meet the goals contained in the NSW HIV Strategy (1).

ACON supports combination approaches to HIV prevention, which include the use of biomedical technologies, risk reduction strategies, increased access to treatment and testing, and ongoing use of condoms and lubricant.

Pre-exposure Prophylaxis (PrEP) is an important addition to the HIV prevention field. ACON accepts that there are a number of unanswered questions about how best to implement PrEP and that the success of PrEP as part of a combination approach depends crucially on its acceptability to those who use it.

It is therefore critical to determine how to obtain the greatest benefit from PrEP and to address structural barriers to access and availability.

Background

ACON acknowledges that condoms and lubricant remains the most effective barrier against the transmission of HIV and the majority of sexually transmissible infections (STIs) (2).

Given that over many years in NSW there has been a consistently high rate of condom use amongst GHAM without any significant reduction in HIV transmission it is apparent that repeated promotion of condom use in itself is not likely to be sufficient to meet the targets outlined in the NSW HIV Strategy 2012 - 2015.

A number of international studies have demonstrated the efficacy of PrEP in preventing HIV acquisition in HIV negative GHAM (3, 4). The preventative effect of PrEP is dependent on a number of variables and its efficacy in trials has varied across different settings and populations.

However, among gay men with access to care and in settings comparable to NSW, and among serodiscordant couples, the efficacy of PrEP has been shown to be very high.

In 2012, the US Food and Drug Administration (FDA) approved Truvada to be used as PrEP by HIV negative people who are at high risk of sexually acquired HIV infection. The US Centre for Disease Control has since developed guidelines and recommended PrEP be used by people at high risk of HIV acquisition via sexual transmission or injection drug use (http://www.cdc.gov/hiv/prevention/research/prep/).

In NSW draft guidelines have been developed, adapted from the CDC guidelines to reflect the local context and health service settings.

The World Health Organisation, in its updated Guidelines On HIV Prevention, Diagnosis, Treatment And Care For Key Populations, released on 11 July 2014 ‘strongly recommends men who have sex

with men consider taking antiretroviral medicines as an additional method of preventing HIV infection (pre-exposure prophylaxis) alongside the use of condoms'.(5)

The guidelines recommend that 'Among men who have sex with men, PrEP is recommended as an additional HIV prevention choice within a comprehensive HIV prevention package (strong recommendation, high quality of evidence).'(6)

However uptake in the USA so far has been low, for a variety of reasons including clinician reluctance to prescribe, lack of clinician confidence (7) and limited knowledge of PrEP among GHAM (8).

The knowledge of, and confidence in, PrEP amongst GHAM and clinicians will need to be improved if PrEP is going to be an effective tool for preventing HIV transmission in NSW.

Around the world, including in Victoria and NSW, a number of PrEP demonstration projects have been initiated to examine the local social, behavioural and epidemiological implications of the implementation of PrEP.

ACON is a partner in the NSW PrEP demonstration project, PRELUDE, that is being led by the Kirby Institute, based at the University of NSW (UNSW). There are also other studies underway that are exploring the possibilities of non-Truvada based regimes, and injectable, long acting forms of PrEP.

To date no drug has been approved for use as PrEP in Australia, nor have any approvals been sought. TGA approval for the use of Truvada as PrEP should be made as soon as possible to ensure that participants in the Australian trials have ongoing access at the point of their completion. This is also important as there will be increased knowledge and interest in PrEP associated with the trials.

Evidence base

In November 2010, results from a randomised, placebo-controlled, clinical trial called iPrEx were released by the US National Institute of Health (NIH). The study looked into the effect of PrEP amongst 2,500 gay and bisexual men and transgender women (9).

The risk of HIV infection was reduced by 44% in men who were given daily Truvada compared with men given the placebo (9). Below optimal adherence levels were observed during the study, with only 51% of the trial participants strictly adhering to their drug regime (9). The study later estimated that if participants had taken their pills every time, the efficacy of the drug regime would have been in excess of 92% (9).

The iPrEx-OLE (Open-Label Extension) study invited all participants from the iPrEx study to take tenofovir/FTC-based PrEP. The efficacy of PrEP was shown to be even higher in this study when compared to the original study. In the group of participants who took at least four doses a week no HIV infection was recorded, translating into a 100% efficacy. The efficacy dropped to 84%, or lower, in people who took the drug 2-3 times per week. (10)

The Partners PrEP was conducted in Kenya and Uganda and explored the efficacy of PrEP in serodiscordant relationships. The results from this study reinforced the findings in the iPrEx study

that Truvada can be an effective biomedical prevention tool. The study results reported that there was a 75% reduction in HIV transmission amongst study participants (11).

PrEP clinical trials have also targeted other high risk groups, such as injection drug users and heterosexuals from high prevalence regions. In the TDF2 study in Botswana, the risk of acquiring HIV among heterosexually active men and women was reduced by 62% among those taking PrEP (12).

The Bangkok Tenofovir Study, which administered a daily dose of tenofovir among injection drug users, demonstrated a 74% reduction in the risk of acquiring HIV, among participants possessing a detectable level of tenofovir in their blood (13).

In the above studies on the efficacy of PrEP, less than optimal adherence to PrEP regimes was strongly associated with an increased risk of HIV transmission. In order to adequately address adherence issues, ACON acknowledges the need for further behavioural studies to explore and better understand factors and contexts which support adherence.

The PRELUDE study in NSW will look at issues of feasibility, acceptability, adherence, side effects and health system costs in the Australian context. The results of this study will further guide the implementation of PrEP in NSW.

Challenges

Cost and access

It is recognised that PrEP could have a considerable impact on the incidence of HIV amongst high prevalence communities, but at a cost (15). Results from the iPrEx study suggest that PrEP could be very cost-effective in terms of the price of an extra year of healthy life for the individual taking it (15).

Researchers suggest that PrEP is most cost effective when targeted at high risk groups. This same research also showed that higher uptake of PrEP amongst high risk groups will result in lower rates of HIV acquisition and therefore reduced onward transmission, resulting in benefits for both the individual taking PrEP and the community (15).

Researchers in PrEP trials overseas have stated that the effectiveness of PrEP in 'real world' settings is highly contingent on individual and social factors, such as personal motivation, a belief that one is at risk, and social and moral attitudes towards PrEP(17).

The Kirby Institute 'TORCH' study investigated the views about, and acceptability of, PrEP held by Australian gay men. It recently concluded and a report on its findings will be published soon. In addition to this, an ongoing study in Victoria aims to explore the social, clinical and epidemiological relationships between gay men at high risk of HIV infection and PrEP (18).

The results from the PRELUDE study, along with these two studies should help identify how we can best implement PrEP to support a comprehensive prevention response among gay men in Australia.

Antiretroviral (ARV) medications are currently subsidised by the Commonwealth Government through the Pharmaceutical Benefits Scheme (PBS). A four-week course of Truvada costs the

Commonwealth Government upwards of $700, though this is for use as treatment for HIV or as post-exposure prophylaxis (PEP).

While the decision of how to fund PrEP is ultimately the responsibility of the Commonwealth Government, ACON will work to ensure that PrEP is affordable and accessible to those who will benefit most from this prevention strategy.

Risk compensation

Some experts have argued that increasing the uptake of ARV for people living with HIV (PLHIV) has led to an increase in risky sexual behaviour amongst gay men (20). They suggest that changes in gay men's sexual behaviour as a consequence of taking PrEP could offset any achieved public health benefits associated with the use of PrEP.

However, a recent study that explored risk compensation within the iPrEx trial suggests that there is no evidence of risk compensation amongst the study participants while taking daily oral PrEP (9). These findings are consistent with studies looking at other preventative options including voluntary male circumcision, vaccines and PEP (21). The iPrEx OLE study found that for most people the use of condoms actually increased, and was associated with an individual's sense of greater control over their own sexual health.

The *PROUD* Study (http://www.proud.mrc.ac.uk) being conducted in the United Kingdom plans to address exactly this issue, exploring whether risk behaviour is different between men taking PrEP and those not taking PrEP. While the results will not be available until 2015, the early findings on effectiveness will result in all participants in the deferred arm being taken off the placebo and offered Truvada.

An Australian study published in 2012 asked GHAM about how PrEP would affect their use of condoms and 92% reported that they would maintain their rates of condom use (8). ACON believes that appropriate use of behavioural health promotion interventions should counteract or ameliorate any possible risk compensation among those taking PrEP.

Research has emphasised that appropriate behavioural interventions should always accompany PrEP use, in order to ensure effectiveness (22). ACON believes people using PrEP should be offered counselling and support services as well as health promotion interventions encouraging GHAM who utilise PrEP to use other preventative tools including condoms and lubricant.

Adherence issues and drug resistance

According to the iPrEx study, self-reported adherence levels above 90% of the time were associated with a reduction in risk for HIV acquisition of 73% (9). Furthermore, when drug testing was performed; a 92% reduction in risk for HIV transmission was found in participants with detectable levels of drug (9). In the iPrEx OLE study, only a third of participants achieved adherence levels of four or more tablets per week. Importantly, the participants most likely to adhere to the treatment guidelines were those most at risk of HIV.
ACON acknowledges that adherence issues will need to be addressed to ensure the success of PrEP as a prevention strategy. Sub-optimal adherence means people run the risk of HIV infection, and the possibility of developing of drug resistance.

ACON has worked with the PRELUDE Study to develop a protocol to ensure that people are given clear messages about the risks of non-adherence so that they are fully aware of the risks of acquiring HIV while taking PrEP compared to acquiring HIV in its absence.

In an attempt to offset any potential adherence and drug resistance concerns associated with PrEP use, the FDA has strengthened the language on Truvada's product label to ensure that health care providers and individuals taking PrEP are aware of both the risks and benefits related to PrEP. This is a strategy that Australia could adopt. It is important to note that, among the seroconversions that occurred during the iPrEx study, none resulted in resistance to Truvada (9).

Intermittent Use

There have been reports of people using PrEP on an intermittent basis. ACON recognises that for PrEP to be an effective tool in the prevention of HIV transmission, people will want to be able to use it in a number of different ways.

It is important that these desired uses are supported by evidence. For most people, PrEP will not be a lifelong prevention tool, but will be used at various stages of life. While this is appropriate, more research needs to be done on intermittent use of PrEP, including providing more data on how long it takes for PrEP to reach a level on the body to provide protective effects and how long these effects last after taking a dose. Until this research is undertaken the full benefits of PrEP may not be realised.

If intermittent use of PrEP is shown to be clinically effective then behavioural research should also be undertaken to understand how best to ensure adequate adherence in the context of intermittent use. Early results from the French and Canadian Ipergay PrEP study (http://www.ipergay.fr) reported that there has been strong adherence to their pericoital pattern of PrEP use, but this study has not released any results on efficacy (23).

Side effects

Long-term side effects of Truvada use for PrEP remain unknown, as participants in the iPrEx study were involved in the trial for less than two years. However research into these side effects is ongoing. Common short-term side effects include headaches, weight loss, diarrhoea, nausea, and fatigue (9).

Nausea in the first month of PrEP use was the most common side effect reported from the iPrEx study. In addition to this, there were no recorded differences in severe or life-threatening side effects between the active and placebo arms of the trial (9). Nausea and other side effects were the most common reason for not participating in the iPrEx OLE study. The interim results of the Ipergay study, with intermittent dosing, have reported much lower reports of common side effects.

There are known side effects associated with longer-term Truvada use for PLHIV, which can include reduced kidney function, renal failure, and reduced bone density. The extent to which Truvada is responsible for such symptoms is not yet known, as HIV infection could play a role in the development of these side effects.

It is also important to note that Truvada can interact with other medications, including some over-the-counter preparations.

Stigma and Discrimination

A recent study from San Francisco identified both positive and negative factors for individuals considering PrEP. Among the social disadvantages, participants identified the social stigma associated with taking PrEP and negative attitudes from healthcare providers.

The stigma and discrimination associated with PrEP use that has been observed in the United States has also been observed in Australia and will have to be addressed if the benefits of PrEP in the community are to be realised.

ACON recognises that a denigration of gay sexual activity is strongly linked with homophobia and internalised shame. We support and promote a positive view of gay men's sexual activity in all its diversity, including the right to access a full range of proven prevention technologies.

Informal use and barriers to information

According to data from the *Sydney Gay Community Periodic Survey*, a small proportion (1.2-2.5%) of gay men in Sydney has been informally using HIV drugs as a preventive measure against the acquisition of HIV in NSW since 2011 (24). It is not known if these men are doing so under the supervision of a doctor or specialist, or are aware of critical issues such as adherence and monitoring for emergence of known side effects.

ACON understands that under s42DL of the *Therapeutic Goods Act 1989* (TG Act) it would be an offence for ACON to publicly advise people on the best way to use Truvada as PrEP. Therefore, people that are using PrEP may not be linked to care and lack access to appropriate support systems that are fundamental for safe and effective use of PrEP. This may have detrimental impacts on the health of the individual and the broader community.

As such, the current regulatory framework appears to be creating the very conditions that might result in harm, which it purports to avoid. ACON will continue to work to ensure that gay men have access to reliable sources of information about their health care choices.

Conclusion

It is ACON's belief, and that of many in the HIV community sector, that the availability of PrEP is an important component of an effective combination prevention response. While questions remain about the optimal implementation of PrEP, we believe that it is essential that these questions be explored and that key stakeholders should act in a timely manner to assess and reach agreement on the availability of PrEP.

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Note: This paper contains general commentary and does not constitute medical advice. You should discuss your particular circumstances with your medical practitioner