Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy that involves HIV-negative people taking anti-HIV drugs to reduce their risk of HIV infection. This strategy also involves regular visits with a service provider to test for HIV and other sexually transmitted infections (STIs), monitor side effects and receive adherence and risk-reduction support. Several randomized, placebo-controlled clinical trials (RCTs) have shown that the daily use of a pill containing the anti-HIV drugs tenofovir and FTC (known by the brand name Truvada) is generally safe and can reduce the risk of HIV infection by over 90% if taken as directed. It is less effective if pills are missed. The daily use of Truvada as PrEP has been approved by the Food and Drug Administration (FDA) in the U.S. Also, the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) have released guidelines recommending that PrEP be offered to HIV-negative people at high risk of HIV infection.

In Canada, Truvada has not been approved for use as PrEP by Health Canada and only Quebec has developed PrEP guidelines for healthcare providers. Because Truvada is currently approved for the treatment of HIV in Canada, healthcare providers can choose to prescribe Truvada for use as PrEP. The prescription of an approved drug for an unapproved use is not prohibited in Canada. This is called off-label use. Research shows that some healthcare providers in Canada are providing PrEP to people at risk of HIV infection.

Putting PrEP into practice

Translating PrEP into a reduction of new HIV infections outside of an RCT setting will be challenging. Slow uptake of PrEP, poor adherence to daily pill taking, and increases in risk behaviour while using PrEP (also known as risk compensation) might limit the public health impact of this strategy. So far, most information on PrEP use has come from placebo-controlled RCTs, in which participants did not know whether they were taking a placebo or PrEP. In these RCTs, risk compensation did not occur and adherence was generally poor. However, use of PrEP in a “real world” setting may be different.

Demonstration projects and “open label” extensions (OLEs) of RCTs are currently ongoing to gain a better understanding of uptake, adherence and risk behaviour outside of a placebo-controlled RCT setting. In these studies, PrEP is being provided in the absence of a placebo and study participants know they are using PrEP (also known as “open label” PrEP use). Information from these demonstration projects and OLEs is beginning to emerge and will be important in guiding the scale-up of PrEP implementation.

Recently, results from the first completed OLE were published and showed that uptake was high, risk compensation did not occur and adherence was a challenge. The results of this study are described below.

The iPrEX OLE study

Between June 2011 and June 2012, the OLE enrolled individuals who had participated in one of three previously completed PrEP RCTs. This included the iPrEX trial and two others. The original iPrEX trial followed almost 2,500 gay men and other men who have sex with men (MSM) and transgender women who have sex with men. It was the first and only trial to show that the daily use of Truvada as PrEP works for these populations. The other two trials were much smaller (enrolled less than 350 MSM in total) and were designed to evaluate safety and feasibility (not effectiveness). Since most participants were expected to come from the iPrEX RCT, this OLE is generally referred to
Participants who enrolled in the OLE were offered “open label” PrEP (daily use of Truvada), free of charge, and were then followed for 72 weeks. Participants could decide to start PrEP immediately or at any time during the first 48 weeks. They did not have to start PrEP to remain in the study. All participants, whether or not they started PrEP, were asked to attend study visits every 12 weeks. During these visits, participants received HIV and STI testing, medical checkups, risk-reduction counselling and (if they were on PrEP) adherence support. For those on PrEP, levels of anti-HIV drugs in the blood were monitored to understand how often participants were taking their pills. The results of these blood tests were shared with the study participants.

The results

Enrollment

Overall, 2,680 RCT participants were contacted and offered enrollment into the OLE; 1,603 (60%) agreed to participate. Those who agreed to OLE participation were more likely to be older, report engaging in condomless receptive anal sex, and have a history of syphilis or herpes compared to those who did not participate. Below are some key characteristics of the OLE participants at the time of enrollment:

- more than 90% were from the iPrEX RCT
- the majority lived in Peru (52%), while the rest resided in the U.S. (18%), Brazil (13%), Ecuador (10%), Thailand (4%) and South Africa (3%)
- 11% were transgender women
- average age – 28 years
- 60% reported engaging in condomless receptive anal intercourse
- 38% had herpes
- 15% had a history of syphilis

Uptake of PrEP

Uptake of PrEP was high. At the beginning of the study, 1,128 (70%) of the 1,603 OLE study participants decided to start PrEP and an additional 97 started PrEP later on in the study. The most common reason for not starting PrEP was concern about side effects. This reason was given by 50% of those who declined PrEP, showing that safety was an important consideration in uptake.

Participants who decided to take PrEP were more likely to have herpes and report engaging in condomless receptive anal intercourse (when they agreed to participate in the OLE, prior to starting PrEP), suggesting they were at higher risk of HIV infection than those who did not take PrEP. Uptake among those at highest risk for HIV infection is important to maximize the public health impact of PrEP as well as its cost-effectiveness. Also, there is less potential for increases in risk behaviour if PrEP users were already engaging in higher-risk behaviours before starting PrEP.

Effectiveness

PrEP helped reduce the number of new HIV infections among those who decided to start it. The rate of HIV infection among PrEP users was 1.8 per 100 person-years. In other words, if you followed 100 of the PrEP users in this study for a year, about two HIV infections would be expected. This rate was 49% lower than the rate of HIV infection among OLE participants who did not decide to start PrEP.

Among PrEP users whose drug levels in their blood suggested they were taking four to seven pills a week, there were no HIV infections. The fact that no transmissions occurred in this group is very encouraging and supports previous research showing that PrEP can be highly effective when taken as directed. However, this finding does not mean that PrEP was 100% effective, as this is statistically impossible to prove. As with any research finding, it is important to consider the role that chance may have played in this result. One way of taking into account the potential effects of chance is to calculate confidence limits. In this study, investigators calculated a lower confidence limit for the effectiveness of PrEP among those with drug levels equivalent to four to seven pills a week. This analysis found that the lower confidence limit was 86%. This means it is very likely that PrEP reduced the risk of HIV infection by more than 86% for study participants who took it consistently.
Adherence

Many PrEP users in the OLE did not take their pills consistently. Drug levels equivalent to taking four to seven pills a week were only present at 33% of study visits and most HIV infections occurred during gaps in PrEP use. Adherence was high during the first few weeks of the study and then decreased over time. While overall adherence was generally low, there was evidence that adherence in the OLE was higher compared to adherence in the RCT phase of the iPrEX study. Adherence was also higher among participants who were older, more educated, had a history of syphilis or herpes, and were engaging in higher-risk sexual behaviours.

It is important to note that low drug levels and gaps in PrEP use can be the result of several factors, including poor adherence to daily pill taking, lack of engagement in PrEP services (such as missed study visits) and PrEP interruptions that study staff knew about. Indeed, PrEP was interrupted 380 times and the most common reasons for interruptions were participant preference (40%) and side effects (24%). The most common side effects leading to PrEP interruption were gastrointestinal-related, such as nausea and abdominal pain.

People at risk of HIV infection can go through periods of higher and lower risk. Greater adherence during higher-risk periods is important for PrEP to protect against HIV infection. However, the factors that put someone at higher risk may be the same factors that make adherence to daily pill taking challenging, such as substance use. In this study, adherence to pill taking was associated with higher-risk sexual behaviours, suggesting that PrEP users were able to identify their HIV risk and respond by using PrEP to reduce this risk. Alcohol, methamphetamine and cocaine use were not associated with lower adherence.

Risk behaviour

There was no evidence of increased risky behaviour (risk compensation) among PrEP users in the OLE. Sexual risk behaviours, such as number of sex partners and frequency of condomless sex, decreased during the study. However, the measurement of these sexual risk behaviours was based on self-report. This measurement method can often be inaccurate because participants may have trouble remembering their behaviours or may not feel comfortable telling the complete truth (for example, participants may say they use condoms more than they actually do). For this reason, study investigators also analyzed the rate of syphilis infections as another way of measuring sexual risk-taking. This analysis found that the rate of syphilis infections was similar between PrEP users and those who didn’t use PrEP. This suggests that PrEP use did not lead to risk compensation.

Moving forward

The results of this OLE have provided important insight into the “open label” use of PrEP and are the first to demonstrate that PrEP can prevent new HIV infections in a “real world” setting.

The uptake of PrEP among MSM and transgender women was high in this study, similar to early experiences from demonstration projects in the U.S. This is in contrast to the uptake of PrEP outside of demonstration projects and OLEs, which has been slow. While surveys of MSM in Canada and the U.S. suggest that interest in PrEP is high, less than 5% in these surveys have actually used PrEP. This discrepancy between high interest and low use suggests that barriers are limiting uptake. Potential barriers include low awareness of PrEP, high cost (about $1,000 dollars per month) and lack of access to a healthcare provider who is willing to prescribe it.

In the iPrEX OLE, some of the above barriers were overcome, as PrEP was offered free of charge by an experienced healthcare provider. Promoting PrEP uptake outside of research studies will require interventions to address these barriers and ensure that individuals who may benefit from PrEP are able to access it. Education about PrEP should emphasize that serious side effects are rare (although little is known about the potential long-term health impacts), as safety seems to be an important consideration for uptake.

The potential for risk compensation has been cited as a concern by policymakers and service providers working in HIV. However, the findings from this OLE suggest that risk compensation may not be an issue, particularly when PrEP is used by people who were already engaging in higher-risk behaviours and when regular risk-reduction support is provided. This emphasizes the importance of combining PrEP use with ongoing risk-reduction support, as well as risk assessments to determine PrEP eligibility.
Unfortunately, adherence to daily pill taking and engagement in PrEP services was a challenge for many participants. Effective strategies to support adherence are needed and several approaches are being evaluated in demonstration projects. Adherence in this OLE decreased over time, suggesting the need for intensification of adherence support as time on PrEP increases.

In addition to reducing the risk of HIV infection, the authors also noted that “making PrEP available provided several indirect benefits, including engagement of people at risk, HIV testing, identification of HIV infection including some acute infections, diagnosis and treatment of sexually transmitted infections, and longer-term counseling.” Interviews of OLE study participants also showed that PrEP had positive effects on mental health by reducing some of the fear, anxiety and guilt associated with “risky” sex and HIV infection.

Overall, the findings from this OLE suggest that PrEP can be safe and effective in a “real world” setting. For PrEP to have a public health impact in Canada, it needs to be combined with strategies to promote appropriate uptake, support adherence and limit risk compensation. Hopefully the insight provided from this OLE can help guide the implementation of PrEP in Canada. Ongoing “open label” studies will provide more information on PrEP use in other populations and settings.

—James Wilton

Resources

Ongoing and planned PrEP evaluation studies  - AVAC

Pre-exposure prophylaxis  - CATIE fact sheet

Moving PrEP into practice: an update on research and implementation  - Prevention in Focus

Truvada approved in the U.S. to help prevent HIV infection  - CATIE News

Uptake of PrEP in the United States  - CATIE News

Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations  - World Health Organization

Preexposure prophylaxis for the prevention of HIV infection in the United States: A clinical practice guideline  - Centers for Disease Control and Prevention

REFERENCES


Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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