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Use of daily Truvada as PrEP is highly effective for gay men in PROUD demonstration project

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Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy that involves HIV-negative individuals taking anti-HIV drugs on an ongoing basis to reduce their risk of HIV infection. Several randomized, placebo-controlled trials (RCTs) have found that the *daily* use of a pill containing the anti-HIV drugs tenofovir and FTC (sold under the brand name Truvada) can reduce the risk of HIV infection in several populations, including heterosexual men and women, gay men and other men who have sex with men (MSM), and people who use injection drugs. While the reduction in HIV risk provided by PrEP in these studies ranged widely (due to varying levels of adherence among study participants), analyses show that PrEP can reduce the risk of HIV infection by over 90% when taken as directed every day. The U.S. Food and Drug Administration (FDA) has approved the daily use of Truvada as PrEP. 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. However, the prescription of an approved drug for another use is not prohibited in Canada. This is called off-label use. Because Truvada is currently approved for the *treatment* of HIV in Canada, healthcare providers can prescribe Truvada for use as PrEP.

Preliminary results from two exciting PrEP studies – known as PROUD and IPERGAY – were recently presented at the Conference on Retroviruses and Opportunistic Infections (CROI) held in Seattle in February 2015. This *CATIE News* discusses the results of the PROUD study, and a subsequent *CATIE News* will review the IPERGAY study.

Effective in the real world?

While PrEP was effective at reducing the rate of HIV infections in several RCTs, less is known about the effectiveness of PrEP outside of such settings, in the real world. Indeed, there are concerns that poor adherence to daily pill-taking and possible increases in HIV risk behaviours (such as condomless sex) could offset the potential benefits of PrEP in a real-world setting.

In the PrEP RCTs, adherence ranged from low to high and HIV risk behaviours did not increase. However, an RCT setting is very different from the real world. For example, RCT participants were "blinded" and did not know whether the pill they were taking was PrEP or a placebo. Also, service providers in RCTs were very well resourced to provide extensive, ongoing HIV risk-reduction and adherence support to PrEP users. Adherence and risk behaviour may be very different in a real-world setting, where PrEP users know the pill they are taking is highly effective against HIV infection and service providers may not have the resources to provide extensive supports.

Demonstration projects are currently ongoing to gain a better understanding of adherence and HIV risk behaviours in the real world. In these studies, PrEP is being provided in the absence of a placebo and study participants know that the pill they are taking is PrEP.

Preliminary results from the PROUD demonstration project in England were presented at the recent CROI. The study found that PrEP did not lead to increases in HIV risk behaviours and that it was highly effective at reducing the rate of HIV infections. The results of this study are described below.

PROUD pilot study

The PROUD study recruited MSM from 13 sexual health clinics in England. Men who were HIV negative and reported more than one condomless anal sex act in the past two months were eligible to participate in the study.

Once enrolled, men were randomized to start PrEP immediately (PrEP group) or delay PrEP use for 12 months (delayed group). The main purpose of the study was to determine the feasibility of enrolling and randomizing approximately 500 men. If feasible, the study investigators planned to conduct a much larger study that would be able to compare the rate of HIV infection between the two groups and measure the effectiveness of PrEP against HIV infection. They did not expect that a study of only 500 people would be large enough to measure effectiveness.

All participants were asked to attend their sexual health clinic every three months. At each visit, participants filled out a behavioural questionnaire and were monitored for side-effects and toxicity, tested for sexually transmitted infections (STIs) and HIV, and prescribed enough Truvada pills for three months. Participants also received adherence and HIV risk-reduction supports, which were part of the routine services offered at the clinics. Little or no additional funding was provided to the clinics for the provision of these supports.

Results

The PROUD study enrolled 545 men between November 2012 and April 2014. Half of the participants were randomized to take PrEP while the remainder had to wait 12 months to start PrEP. The average age of participants was 35 and most of the men were white (81%), employed (71%), educated at the university level (60%), and single (54%).

Many clinical trials have an independent oversight committee called a Data and Safety Monitoring Board (DSMB) or Independent Data Monitoring Committee (IDMC). The role of these committees is to periodically review the data collected from a study and to stop or modify the study if there are concerns about the safety of participants.

In October 2014, the PROUD IDMC recommended that men in the delayed group be offered PrEP. This recommendation was made because it was clear that participants in the PrEP group were at much lower risk of HIV infection. Therefore, it was considered unethical to continue delaying PrEP initiation.

Effectiveness

Prior to offering PrEP to those in the delayed group, there had been three HIV infections in the PrEP group and 19 in the delayed group. The investigators noted that two of the three HIV infections in the PrEP group may have been in men who were already HIV positive when they started PrEP.

The rate of HIV infection in the delayed group was much higher than the study investigators expected (for every 100 participants followed for a year, nine infections occurred). This was why the study was able to measure effectiveness, and a larger study was not needed.

The rate of HIV infection among men in the PrEP group was 86% lower than the rate in the delayed group, demonstrating that PrEP was highly effective at reducing HIV risk.

Adherence

Little data on adherence to pill-taking was presented at the conference, although it must have been high to observe such a dramatic reduction in HIV risk. Overall, the service providers in the study prescribed enough pills to cover 86% of the days that participants were in the study (some participants ran out of pills because they missed a clinic visit). Two of the three HIV infections in the PrEP group occurred in participants who had missed several study visits and were likely not taking pills at the time of HIV infection. In a small subset of men who said they took pills consistently, all of them had drug levels in their blood.

Risk behaviour

There was no definitive evidence that HIV risk behaviours were higher among participants who were taking PrEP. According to self-reports there was no increase in condomless sex or number of sex partners during the study. The proportion of participants who became infected with an STI in the PrEP group was slightly higher than in the delayed group (57% vs. 50%). This suggested that HIV risk behaviours may have increased as a result of PrEP use.

However, this difference was not statistically significant, and may have been due to the higher number of STI tests conducted among those using PrEP.

Use of post-exposure prophylaxis (PEP)

PEP refers to the daily use of anti-HIV drugs for one month after an exposure to HIV. It is different from PrEP as it is started as soon as possible, within 72 hours of being exposed to HIV, and is only meant to reduce the risk from a single, accidental exposure. In the PROUD study, PEP was available to participants and its use was high among men in the delayed group. Overall, 31% of these men accessed PEP and some used it more than once (there were a total of 174 PEP prescriptions). However, the rate of HIV infection remained high despite the relatively frequent use of PEP.

Conclusion

The PROUD study demonstrated that the use of daily Truvada as PrEP can be highly effective at reducing rates of HIV infection outside of an RCT setting. The study investigators concluded that "concerns that effectiveness would be undermined in a real-world setting were unfounded."

Encouragingly, the level of HIV risk reduction in PROUD was higher than previously observed in other PrEP studies. The highest HIV risk reduction observed in an RCT was 75% among heterosexual serodiscordant couples in the Partners PrEP study. The only other real-world study to measure PrEP effectiveness was the iPrEX open label extension (OLE), in which the rate of HIV infection was 49% lower among gay men and other MSM using PrEP.

The dramatic reduction in risk of HIV infection in the PROUD study demonstrates that high levels of adherence to daily pill-taking can be achieved in a real-world setting. Further, HIV risk behaviours did not appear to increase. It is reassuring that the high rate of STIs among men in the study did not offset the benefits of PrEP, as STIs are known to increase the risk of HIV infection. However, it is important to note that men in the PROUD study received regular STI testing, which ensured timely diagnosis and treatment of these infections. These services may have helped mitigate the impact of STIs on their risk of HIV infection.

The very high rate of HIV infection among men in the delayed group – despite the provision of risk-reduction supports and high PEP use – emphasizes the need for additional HIV prevention strategies, such as PrEP. It also shows that gay men at high risk of HIV infection can be identified by service providers and that they are interested in using PrEP. Hopefully the PROUD study results can help guide the implementation of PrEP in Canada. Ongoing real-world 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 (PrEP) – CATIE fact sheet

PrEP use in the "real world": Results from the iPrEX open label extension – *CATIE News*

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

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

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