Summary

Oral pre-exposure prophylaxis, or PrEP, is a way for an HIV-negative person who is at risk of HIV infection to reduce their risk of getting HIV by taking antiretroviral drugs. Oral PrEP contains two antiretroviral drugs: tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). The daily use of oral PrEP is approved by Health Canada to reduce the risk of the sexual transmission of HIV in combination with safer sex practices for people at high risk of HIV infection. Use of oral PrEP involves regular medical appointments for monitoring and support. Oral PrEP is a highly effective HIV prevention strategy when used consistently and correctly. It is generally safe and well-tolerated, and is available by prescription from physicians in Canada.

What is oral PrEP?

Oral PrEP involves the use of antiretroviral drugs by an HIV-negative person to reduce their risk of becoming infected with HIV. Oral PrEP is taken in pill form, starting before being exposed to HIV and continuing afterwards. Oral PrEP contains two antiretroviral drugs that are also used for HIV treatment: tenofovir (also called TDF) and emtricitabine (also called FTC).

The daily use of TDF and FTC as oral PrEP has been approved by Health Canada to reduce the risk of the sexual transmission of HIV in combination with safer sex practices in people at high risk for HIV infection. This approval did not include transmission through injection drug use. However, daily oral PrEP is recommended by the Centers for Disease Control and Prevention (CDC) in the United States and by the World Health Organization (WHO) to reduce the risk of HIV transmission in people at high risk through sexual activities and injection drug use.

How does oral PrEP work to help prevent HIV?

PrEP interferes with the pathways that HIV uses to cause a permanent infection. For HIV to cause infection the virus must gain entry into the body, infect certain immune cells, make copies of itself (replicate) within these immune cells, then spread throughout the body.

When oral PrEP is taken consistently and correctly, antiretroviral drugs get into the bloodstream and genital and rectal tissues. The drugs work to help prevent HIV from replicating within the body's immune cells, which helps to prevent a permanent infection.

For PrEP to help stop HIV replication from happening, drug levels in the body must remain high. If pills are not taken consistently as prescribed there may not be enough medication in the body to reduce the risk of HIV infection.

How well does daily oral PrEP work?

There is evidence from randomized clinical controlled trials (RCTs) that daily oral PrEP is a highly effective strategy to reduce the risk of the sexual transmission of HIV if taken consistently and correctly as part of a comprehensive prevention package in gay men and other men who have sex with men (MSM) and in heterosexual men and women. In addition, limited evidence from one RCT found that daily oral PrEP (with tenofovir alone), when used consistently and correctly, is effective at reducing the risk of HIV transmission among people who inject drugs.

In all the clinical trials, PrEP was provided as part of a comprehensive prevention package that included regular testing and treatment for sexually transmitted infections (STIs), free condoms and ongoing behavioural counselling.

Adherence (taking medications exactly as prescribed) is crucial for oral PrEP to work. The evidence shows that higher adherence is associated with greater protection.

Before taking adherence into account, the overall risk reduction provided by a daily oral PrEP regimen in RCTs ranged from zero to 86%. All of these studies evaluated the sexual transmission risk except for one, which found a

49% overall risk reduction in people who inject drugs. The wide range of protection observed in these trials has been explained by varying levels of adherence to daily pill taking.

To demonstrate the importance of adherence, additional analyses in these trials looked at drug levels in the blood of people who were taking oral PrEP consistently compared to those who were not. These analyses found that daily oral PrEP reduced the risk of HIV transmission by between 85% and 92% among MSM and heterosexual men and women who took the drug consistently compared to those who did not. In people who inject drugs, daily oral PrEP with tenofovir alone reduced the risk of HIV transmission by 84% among people who used the drug consistently compared to those who did not.

The daily use of oral PrEP has also been evaluated in "open-label" studies, predominantly among MSM. In these types of studies, no placebo is used and all participants know they are taking PrEP and that it is effective at preventing HIV transmission. These studies support the finding that oral PrEP is highly effective at reducing HIV transmission when taken consistently and correctly. One open-label study found that the risk for HIV was reduced by 86% overall among MSM who were taking daily oral PrEP compared to those who were not. In open-label studies, adherence to daily pill taking was higher than in RCTs.

There are several well-documented cases of PrEP failure in people who were adherent to PrEP. In two of these cases, men taking PrEP acquired a rare strain of HIV that was resistant to the drugs in PrEP. In a third case of PrEP failure, a gay man acquired a strain of HIV with no drug resistance, and the reason why PrEP failed is unclear. Over an eight-month period of PrEP use, he had many anal sex partners where no condoms were used, experienced episodes of rectal STIs, and used drugs during sex.

This highlights that PrEP does not work 100% of the time, however these are very rare events. In all three cases, the men who became HIV positive were able to diagnose their HIV early and get on treatment immediately because they were on PrEP and having regular medical check-ups.

Does on-demand PrEP work?

Evidence suggests that intermittent, or on-demand, PrEP reduces the risk of HIV transmission among MSM. One RCT, known as IPERGAY, evaluated the use of on-demand PrEP among MSM. No studies have been conducted in other populations.

In the IPERGAY trial, MSM were to take two pills two to 24 hours before first sexual activity, followed by one pill taken daily until 48 hours after the last sexual activity. The RCT phase of IPERGAY found an 86% reduced risk of HIV infection among MSM in the on-demand PrEP group compared to those in a placebo group (two participants in the PrEP arm became infected). Men in the RCT phase of this study had sex frequently and – as a result – took their pills on a regular basis (four pills a week on average). IPERGAY continued as an open-label extension with all participants offered on-demand PrEP. Results from the open-label phase showed that one more HIV transmission occurred in 362 participants, over 515 person-years of follow-up (equivalent to following 515 people for one year). None of the three participants who became infected over the entire course of the study had PrEP detected in their blood, which means they were likely not adherent. On-demand PrEP has only been evaluated in MSM and is not recommended for people who have vaginal sex or people who inject drugs.

On-demand oral PrEP is not approved by Health Canada; however, on-demand PrEP can be prescribed 'off label' by physicians as an alternative form of PrEP that can be considered for use for MSM only.

Does oral PrEP work as well for women as for men?

Evidence from RCTs suggests that oral PrEP is as effective for women as it is for men when used consistently and correctly, but adherence may be more important for women.

There were initial concerns that PrEP may not work for women because two RCTs did not find a reduced risk of HIV in heterosexual women taking daily oral PrEP. However, adherence was very low in these studies with only a small proportion of women taking PrEP daily.

There is some evidence showing that the drugs in PrEP take longer to reach maximum levels in vaginal tissues compared to rectal tissues, and that drug levels are lower in vaginal tissues. This suggests that daily dosing of oral

PrEP may be more important for women having vaginal sex to maintain sufficient drug levels to help prevent HIV infection.

Who should take PrEP?

PrEP can be used by people who are HIV negative and at high risk for HIV infection. The World Health Organization recommends that PrEP may be indicated for people who are HIV negative and:

- Have a sexual partner with HIV who is not on treatment or not virally suppressed

OR

- Sexually active in a high HIV incidence/prevalence population AND any of the following:
  - Has condomless vaginal or anal sex, or
  - Has a sexual partner with one or more HIV risk factors, or
  - Has a history of sexually transmitted infection in the past six months, or
  - Use of post-exposure prophylaxis (PEP), or
  - Requesting PrEP.

What else is involved with taking oral PrEP?

Oral PrEP is part of a comprehensive HIV prevention strategy that includes safer sex practices and routine medical appointments.

The first step is to make sure a person is HIV negative before starting PrEP. They will also need to be tested for hepatitis B and other STIs and have their kidney function checked.

A person using oral PrEP needs to take it as prescribed by their healthcare provider. In addition to taking the medication as prescribed, they must also attend regular doctor's appointments, approximately every three months. These regular visits are necessary in order to be tested for HIV and other STIs, monitored for drug side effects, and receive ongoing adherence and risk-reduction counselling.

Is PrEP intended to replace condoms and other HIV prevention strategies?

Oral PrEP is not intended to replace other HIV prevention strategies because it is not 100% effective, is substantially less effective if used inconsistently or incorrectly, and is not intended for everyone. PrEP can still be effective at reducing the risk of HIV infection when condoms are not used; however, guidelines recommend that PrEP be used in combination with safer sex practices and harm-reduction strategies to optimally reduce the risk of HIV infection.

PrEP only helps to prevent HIV and does not offer protection against STIs (such as herpes, chlamydia or syphilis) or blood-borne infections such as hepatitis C. Other prevention strategies (such as using condoms or new injection equipment) are needed to reduce the risk of all other infections that can be passed through sex or sharing of injection drug use equipment.

What are the advantages of PrEP?

The main advantage of oral PrEP is that it adds another highly effective HIV prevention option to the growing list of prevention strategies. For example, PrEP may provide another method to help protect people who are unable to negotiate condom use with their partner(s), people in serodiscordant relationships (where one partner is HIV negative and the other is HIV positive), people who inject drugs but are not able to obtain new injection equipment, or other people who do not use condoms or new injection equipment consistently for whatever reason.

Another advantage is that oral PrEP use can be started during periods of higher risk and stopped during periods of lower risk.

What are some of the safety concerns associated with taking PrEP?

Drug resistance

A person can develop resistance to the drugs in PrEP if they are HIV positive (and unaware of their positive status) when starting oral PrEP. Drug resistance can limit a person's future treatment options, so it is important to ensure that they are HIV negative before starting oral PrEP.

A person can also develop drug resistance if they become HIV positive while taking oral PrEP. In clinical trials, the risk of developing drug resistance was low for people who were HIV negative when starting PrEP.

Regular HIV testing is necessary while taking oral PrEP. If a person using PrEP becomes infected with HIV, PrEP use must be discontinued as soon as possible, to reduce the risk of developing drug resistance. If a person's HIV becomes resistant to the drugs in PrEP, those same drugs may not work to treat HIV.

Side effects

Oral PrEP may cause side effects, which may negatively affect a person's quality of life and ability to adhere to their medication schedule.

Although TDF and FTC are generally better tolerated than some of the other drugs used to treat HIV, they are still capable of causing side effects. Some of the possible side effects include nausea, vomiting, diarrhea, headache and dizziness. In clinical trials these side effects were generally mild, temporary, and only affected between 1% and 10% of participants. PrEP may also cause small decreases in kidney, liver and bone health. In oral PrEP trials this did not lead to kidney or liver failure or bone fracture, and the changes were reversible after stopping PrEP.

Although research suggests that the use of oral PrEP is generally safe and well tolerated, the long-term effects of using PrEP are less well known.

How can people at high risk of HIV infection access PrEP?

How can people at high risk of HIV infection access PrEP?

An HIV-negative person who wants to take PrEP needs to get a prescription from a doctor who is willing to provide the necessary medical follow-up in a safe and informed way. Health Canada has approved the prescription of TDF and FTC as PrEP for reducing the risk of sexually acquired HIV infection, in combination with safer sex practices.

Not all doctors are knowledgeable about PrEP and it may be difficult for clients to find a doctor who is willing to prescribe PrEP for HIV prevention.

Although the use of PrEP has not been approved by Health Canada to reduce the risk of injection-related HIV transmission, healthcare providers can still prescribe it for this purpose. This is possible because the drugs have already been approved for reducing the risk of sexual HIV transmission and for treatment of HIV. When an approved drug is prescribed for an unapproved use, this is called an "off-label" prescription. These types of prescriptions are legal and – for some types of drugs – common.

Antiretroviral drugs are expensive and oral PrEP can cost between $250 and $1000 a month. Currently, only some private and public health insurance plans in Canada will cover the cost of the drugs. PrEP was approved for prevention in Canada in February 2016 and we expect that more insurance coverage will eventually become available. Advocacy may be needed to get PrEP covered by all provincial, territorial and federal drug programs to ensure that people who need PrEP can access it.

What other types of PrEP are out there?

Other types of PrEP, including vaginal or rectal gels, intravaginal rings and long-lasting injections are currently in experimental stages. No other forms of PrEP have been approved for use by any regulatory agency in the world, and we do not expect them to be available for use in Canada in the near future.

Resources

CATIE statement on the use of oral pre-exposure prophylaxis (PrEP) as a highly effective strategy to prevent the sexual transmission of HIV

Oral pre-exposure prophylaxis: putting a new choice in context – UNAIDS

Preexposure prophylaxis for the prevention of HIV infection in the United States – U.S. Centers for Disease Control and Prevention (CDC)

Guideline on when to start ART and on pre-exposure prophylaxis for HIV – World Health organization (WHO)

Avis intérimaire sur la prophylaxie préexposition au virus de l'immunodéficience humaine, Ministère de la Santé et des Services sociaux du Québec (French only)

Guidance for the use of Pre-Exposure Prophylaxis (PrEP) for the prevention of HIV acquisition in British Columbia – BC Centre for Excellence in HIV/AIDS

European AIDS Clinical Society Guidelines

WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection

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