Interagency Coalition on AIDS and Development
Coalition Interagence sida et développement

PRE-EXPOSURE PROPHYLAXIS (PREP) AS A POTENTIAL HIV PREVENTION METHOD

Introduction

Research into new prevention technologies (NPT) is a critical part of comprehensive HIV prevention. NPTs are needed for those who cannot use or rely on existing prevention methods such as condoms. One technology currently being tested in clinical trials is pre-exposure prophylaxis (PrEP), an experimental technology that would use antiretrovirals (ARVs) to protect HIV-negative people from HIV infection[1] . The science is quite advanced and initial results from PrEP trials are expected as early as 2010.

PrEP could prove to be an important opportunity in the field of HIV prevention, yet there are many ethical and practical concerns that need to be addressed as the research moves forward. Currently, there is limited dialogue around these issues and the impact that PrEP trial results will have in Canada and globally. It is important that Canadians develop an understanding of PrEP and related issues so that they are able to participate in a global dialogue and assess if or how PrEP could benefit Canadians. This fact sheet provides an overview of PrEP research and raises some of the concerns and unanswered questions that require discussion among a broad group of stakeholders.

PrEP Research

PrEP as part of comprehensive prevention

Currently, there are several proven HIV prevention options that we have at our disposal, including male and female condoms, behaviour change counseling, male medical circumcision[2], and the use of safe injecting equipment. While these tools exist, access to them is limited. For example, only 9% of sexually active people have access to male condoms, and access to female condoms is even lower[i]. Such dismal statistics point both to the urgent need to scale up access to proven prevention strategies, and to the need to invest in the research and development of new prevention technologies (NPTs).

NPTs, including PrEP, are not expected to replace other proven prevention options. In fact, it is unlikely that PrEP would be as effective as condoms. However, PrEP could be used in combination with condoms or other proven prevention options to boost effectiveness. In addition, PrEP could offer an important option for people who cannot or chose not to use existing prevention options consistently. Unlike condoms, PrEP would not require the consent of a partner. This could be of particular importance to women who are often unable to negotiate condom use with their partners.

Evidence to support PrEP research

At present we do not know whether PrEP will work to prevent HIV. If it is proven effective, it may reduce the chances that an HIV-negative person who is taking the antiretrovirals will become HIV-positive if they are exposed to the virus.

There are a number of reasons why researchers think that PrEP could work. Studies done in non-human

[1] In this fact sheet, we will be discussing PrEP as ARVs that are administered orally, although it is important to note that some literature also refers to topical ARV-based microbicides as PrEP.

[2] Research has shown that circumcised men have a 50 to 60 percent reduction in their risk of acquiring HIV through vaginal sex. It has not shown that circumcision makes a man less likely to transmit HIV to his partner through vaginal sex, nor has it shown to lower the risk of transmission for either men or women during anal sex.

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primates have found that pre-treatment with ARVs significantly reduces the risk of infection with simian immunodeficiency virus (SIV) and SHIV. SIV is the monkey equivalent of HIV, and SHIV is an engineered combination of SIV and HIV that more closely resembles HIV. In one study comparing monkeys that were given PrEP to those that were not, and then exposed to SHIV, all but one of the monkeys not receiving PrEP became infected, but only between 20 and 50% of monkeys receiving PrEP contracted SHIV .

The use of ARVs in reducing vertical transmission of HIV is another reason for anticipating that PrEP might work. Giving ARVs to HIV-positive pregnant women during labour and delivery, and to their newborn babies after delivery and during breastfeeding, has been shown to significantly reduce the transmission of HIV from mother to child.

Finally, there is evidence that taking ARVs soon after exposure to HIV—post-exposure prophylaxis (PEP) —reduces the likelihood of infection.

The research process

As discussed above, PrEP studies in animal models have demonstrated a reduction in transmission of SIV and SHIV. Researchers are now testing PrEP for safety and effectiveness in humans. While safety trials are still underway, most of the current trials are efficacy trials—trials that measure whether or not PrEP actually works to prevent HIV. Because ARVs are already used in treatment, a great deal of safety data already exists. However, further studies will be required to address questions of safety in adolescents and pregnant women, two populations not currently involved in PrEP trials.

In PrEP efficacy trials, measures are taken to reduce the risk of participants becoming infected. All participants are provided with a standard prevention package including testing and treatment for sexually transmitted infections, male and female condoms, and behaviour change counseling. Participants are regularly reminded that they do not know whether they are on the experimental drug or on a placebo (a pill that has no effect on the body or on HIV). As we know, even with information and services, people are not always able to protect themselves all the time and some participants will become infected throughout the trial. The number of infections in the group that has received the experimental drug is compared to the number of infections in the group that received the placebo drug. The difference between these numbers indicates whether or not PrEP has significantly reduced the risk of HIV infection.

The trial is responsible for making arrangements so that trial participants who become HIV-positive during the trial are assured of getting ongoing access to ARVs when they need them—either through referrals to treatment programs, or from the trial itself.

If safety and efficacy trials are successful, introductory studies will be conducted. Through introductory studies, PrEP will first be available to people who participated in PrEP trials, and possibly other groups at high risk of HIV infection. National regulators will then review the product and decide whether to approve it for marketing in their countries. Post-surveillance marketing systems will monitor the impact that PrEP is having, and will track large numbers of users to see the impact PrEP has on their bodies over a long period of time. It will also be important to monitor how people are using PrEP in real life, outside of clinical trials.

Current PrEP trials

Two ARVs are currently being studied as PrEP—tenofovir disoproxil fumarate (TDF) (marketed by the name Viread) and a combination of TDF and emiticitabine (FTC) (marketed by the name Truvada). In the future other drugs may also be tested as PrEP. TDF and TDF/FTC are considered good PrEP candidates as they stay in the bloodstream for a long time and require a person take only one pill a day. In addition, these drugs have caused few side effects in HIV-positive people taking them for treatment, and so far appear to be safe for HIV-negative people. Finally, these two drugs are both from a particular class of ARVs called

nucleoside analogs. Usually, HIV that is resistant to one ARV from a particular class will be resistant to others from that same class; however, this does not occur with TDF and TDF/FTC. Other ARVs from the nucleoside analog class can still be used if resistance to these two drugs develops.

PrEP studies are being conducted with several different populations—men who have sex with men (MSM), people who use injecting drugs, heterosexual men and women in high-prevalence locations, and serodiscordant heterosexual couples (meaning one partner is HIV-positive and the other is HIV-negative). PrEP may work better in one population than another, based on how people are exposed to HIV (by sex or by needles), how often they are exposed, and to what extent PrEP affects their level of risk.

Trials are taking place in the US, Africa, Latin America and South-East Asia. One study taking place is an expanded safety study involving 400 MSM. This study is investigating side effects, adherence, and the impact of PrEP on risk-taking behaviours. In addition, six efficacy studies are underway. One of these studies will compare PrEP taken in a pill to a topical tenofovir gel. These studies involve from 1,200 to 5,000 individuals each. Results from these trials will be available between 2010 and 2012. Another study being planned will involve 150 participants and will evaluate the feasibility of PrEP that is taken twice weekly and before sex, rather than daily. Since we do not know how well people will adhere to a daily pill outside of clinical trials, it is important that researchers study whether or not alternative dosing schedules would be effective.

Investment in PrEP research

Over the last seven years, global public sector and philanthropic investment in PrEP totaled US$119 million. Between 2005 and 2008, investment in PrEP increased by US$32 million (255%)[ii].

The majority of PrEP funding comes from the Bill and Melinda Gates Foundation, the US National Institutes of Health (NIH), the US Centers for Disease Control and Prevention (CDC) and the US Agency for International Development (USAID). In addition, Gilead, the manufacturer or TDF and TDF/FTC, has provided in-kind support for PrEP research.

Important Issues for Consideration

The threat of drug resistance

One of the central concerns with PrEP is the threat of drug resistance. The concern is that people who become unknowingly infected with HIV while taking PrEP (either due to PrEP's partial efficacy or to poor adherence) will continue to take the drugs once they have become infected. This could lead to the development of drug-resistant strains of HIV and compromise an individual's treatment options over the long-term. If an individual becomes infected while taking PrEP and develops drug resistance, this resistance will also impact anyone the individual transmits the virus to. Drug resistance is of particular concern for developing countries where HIV-positive people have limited or no access to second line drugs once resistance to first line drugs develops.

Careful planning for the roll-out of PrEP will be crucial to minimize the threat of drug resistance. Planning will have to address questions around the frequency and process for routine testing of people using PrEP, as well as initial testing to ensure that PrEP users are HIV-negative to begin with.

Behavioural disinhibition

Another concern that arises with the introduction of new prevention technologies is whether risk behaviour will increase among those using the new prevention measure. Although PrEP will not likely be 100% effective, PrEP users may feel protected and therefore increase their risk behaviour. This phenomenon is referred to as behavioural disinhibition, or risk compensation. The impact of behavioural disinhibition will depend on several factors, including the level of

efficacy of the new product—the higher the efficacy, the less behavioural disinhibition is a concern.

The threat of behavioural disinhibition points towards the critical need for discussing acceptable levels of efficacy, communicating accurate information about PrEP and partial efficacy, and counseling individuals who are candidates for PrEP.

Ethics of ARVs as prevention

An important issue to address when considering PrEP is the ethics of using ARVs for prevention when in 2008 only 42% of those in need of treatment in low- and middle-income countries were able to access it[iii]. This is a complex question, with no easy answers. It requires ongoing dialogue that examines the issue from both a domestic and a global perspective, and includes the voices of many stakeholders, including people living with HIV and prevention advocates.

Adherence

PrEP researchers need to continue asking questions about how PrEP will be used in the real world among different populations. Among other things, adherence to PrEP will be impacted by the level of side effects people are willing to accept in preventive measures, and whether people are able to comply with the dosing regimen.

One particular question that arises in relation to PrEP is whether it would be effective if only taken intermittently, rather than daily. This is a critical question as we know that people are likely to use PrEP differently in real life than in a clinical trial. One study underway is looking at the effectiveness of PrEP when taken twice weekly and before sex. This is referred to as "routine plus event-based dosing". Other dosing possibilities may also be researched in the future, including "weekly-based dosing" and "event-based dosing". Event-based dosing would mean taking tenofovir or Truvada based on specific exposure events, i.e. before sex is anticipated and/or after it happens.

It is also necessary to consider that people may want to go on and off PrEP at different periods of their lives, referred to as "periodic dosing". It is unknown what impact this would have on effectiveness.

Access

Access to PrEP poses another series of challenges. Because PrEP users must be HIV-negative, it will be important that potential users are first tested for HIV. Those who test negative and choose to begin taking PrEP will need to be tested regularly to ensure that they have not become infected while taking PrEP, and thus risk developing drug resistance, as discussed above. The need for expanded testing would clearly be a challenge for the successful roll out of PrEP. In Canada, approximately 27 % [iv]of people infected with HIV do not know they are infected, and in southern Africa it is estimated that between 80 and 90%[v] of people with HIV do not know they are infected.

Further, access to ARVs requires access to a prescriber. In countries where health systems are weak or overburdened, this will be of particular concern. The need to access a prescriber may also influence which groups are able to access PrEP, as well as levels of adherence.

When considering access, it is important to address questions about which populations are the best candidates for PrEP interventions in Canada and globally, and what impact targeted interventions will have on stigma. It is also important to address the particular challenges that different populations will face in accessing and adhering to PrEP.

Finally, it is critical to think about who will be involved in decisions about how PrEP is allocated, globally and in Canada. It is crucial that stakeholders that will be involved in providing and/or limiting access to PrEP are engaged in discussions about its potential roll-out. It is also important to consider the possibility and consequences of unintended access to PrEP. For example, it is possible that PrEP could be sold on the

informal market to those who do not want to undergo HIV testing.

Safety concerns

The drugs being tested for use as PrEP—tenofovir and Truvada—have so far been found to cause few side effects among HIV-positive and HIV-negative people. Still, there are a number of safety issues that are of particular concern.

In addition to being a treatment for HIV, tenofovir is also a treatment for hepatitis B, a relatively common sexually transmitted infection. If someone with hepatitis B were to go on and off tenofovir, this could cause problems, including serious, possibly life-threatening flares of hepatitis B. Anyone considering taking PrEP should be tested for HBV, and offered HBV vaccination if they are not infected. The potential effect of PrEP on people with hepatitis C is unknown, and requires further research.

Among a small percentage of people (mostly those with pre-existing kidney impairment and with high blood pressure), taking tenofovir-based drugs can cause kidney problems. Similarly, for people with bone density loss, tenofovir-based drugs could worsen the problem. The effect of PrEP on post-menopausal women and young adults should be studied carefully to assess the impact on osteoporosis and bone formation.

More data is also needed around drug safety during pregnancy and breastfeeding, and how the drugs affect people with relatively lower body weight, including women.

Conclusion

If found to be safe and effective, PrEP has the potential to contribute significantly to a comprehensive response to HIV. However, there are many practical and ethical challenges that need to be addressed while research is still ongoing. It is imperative that Canadian stakeholders become informed about PrEP and the related issues in order to ensure that Canadians can contribute to an informed global dialogue and engage in discussions about the appropriateness of PrEP in the Canadian context. With trial results expected starting in 2010, there is an urgent need for Canadian stakeholder involvement.

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[i] Global HIV Prevention Working Group. 2008. *Bringing HIV prevention to Scale: An urgent global priority.* http://www.globalhivprevention.org/pdfs/PWG-Scaling-Up-ExecSumm.pdf

[ii] HIV Vaccines and Microbicides Resource Tracking Working Group. 2009. *Adapting to Realities: Trends in new HIV prevention research funding 2000 to 2008.* www.hivresourcetracking.org

[iii] World Health Organization. 2009. *Towards universal access: Scaling up priority HIV/AIDS interventions in the health sector.* http://www.who.int/hiv/mediacentre/tuapr2009_km_en_a4.pdf

[iv] Public Health Agency of Canada. 2007. *HIV/AIDS Epi Update*. http://www.phac-aspc.gc.ca/aids-sida/publication/epi/pdf/epi2007_e.pdf

[v] The Lancet Student. *An interview with Kevin De Cock, Director of WHO's HIV/AIDS department.* http://www.thelancetstudent.com/2008/01/29/an-interview-with-kevin-de-cock-director-of-whos-hivaids-department/

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