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Truvada for HIV prevention - some good news but caution is still needed

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As we enter the fourth decade of the AIDS pandemic, the spread of HIV seems to have slowed compared to the 1980s. However, there has been a resurgence of new HIV infections among men who have sex with men (MSM), particularly in Canada, Australia, Western Europe and the United States. A renewed and enhanced focus on HIV prevention is urgently needed if the spread of HIV among MSM is to be slowed. Such a focus is important because while HIV treatment is readily available in most high-income countries, there is no cure. Furthermore, the ultimate prevention tool—a highly effective HIV vaccine—is unlikely to become available within the next 10 years. Prevention interventions that work in the short- and medium-term in heterosexual men in Southern Africa, such as circumcision of the penis, are unlikely to have a major impact on the spread of HIV among MSM. So, for now and the foreseeable future, promoting safer-sex, including the correct and consistent use of condoms, remains essential to the prevention of HIV among all sexually active people, including MSM.

Researchers have been trying to find other ways to reduce the risk of HIV transmission particularly among MSM. One additional safety mechanism could be to give HIV-negative men anti-HIV drugs to protect them from HIV infection should they be exposed to the virus during sex. Taking medicines before and after potential exposure to HIV to prevent infection is called pre-exposure prophylaxis, or PrEP.

On 23 November, 2010, the results of the first clinical trial of an oral form of PrEP were released.

iPrEx

iPrEx is an international study of the use of Truvada [tenofovir + FTC (emtricitabine)] as a form of PrEP among MSM. The study enrolled almost 2,500 HIV-negative MSM. Half of the men were given Truvada and the other half were given a placebo. On average study participants were monitored for a little over one year. Researchers found that daily Truvada reduced the relative risk of new HIV infections by about 44%. This is promising but imperfect. This clinical trial and several other related issues are discussed in this *CATIE News* bulletin.

Study details

Between July 2007 and December 2009, 2,499 HIV-negative MSM were recruited for the iPrEx study in the following countries and regions:

- South Africa
- South America (Brazil, Ecuador, Peru)
- Thailand
- United States

All participants were randomly assigned to take a pill containing either Truvada or placebo each day. Participants were regularly monitored at clinic sites and were provided with the following comprehensive prevention services:

- rapid HIV testing
- HIV risk-reduction counseling
- testing and when necessary, treatment for common sexually transmitted infections (STIs), including gonorrhea, herpes and syphilis

Adherence counseling, to help participants to take the study medications exactly as prescribed, was also provided at every visit.

Every 24 weeks all participants were screened for additional STIs and treated when necessary. Partners of participants were also offered treatment for STIs. All participants who were at risk for hepatitis B virus were offered vaccination against this infection. Participants were monitored for an average of 1.2 years.

The average profile of participants when they entered the study was as follows:

- age—27 years
- all participants were born male but 29 (1%) of the study participants identified as female
- number of partners in the past 12 weeks—18 men
- proportion of men having unprotected anal intercourse in the past 12 weeks—60%
- proportion of participants who had engaged in trading sex for money in the past 12 weeks—41%
- rates of syphilis (13%) and herpes (36%) were similar in participants assigned to the Truvada and placebo groups

It should be noted that this is a very high risk group of MSM, many of whom did not have access to comprehensive HIV prevention services prior to enrolling in the study.

Results—Effectiveness

During the study, 100 of the study participants developed new HIV infections. The new HIV infections were distributed as follows:

- Truvada recipients—36
- placebo recipients—64

This represents a *relative* reduction of the risk of HIV infection by 44% because of Truvada. This result was statistically significant.

The *absolute* reduction in risk of infection as a result of taking Truvada was about 2% over 100 person-years. This means that if 100 MSM at high risk for HIV infection took Truvada for one year, an estimated 2 new HIV infections would be prevented.

The following factors had no significant impact on the effect of Truvada:

- age
- alcohol use
- education level
- ethnicity or race
- whether or not participants were circumcised

Results—Impact on HIV disease

Some researchers had hoped that when HIV infection did occur among Truvada users, this drug might have a beneficial effect, perhaps reducing the severity of HIV infection. However, among people taking Truvada who did become infected, the amount of HIV in their blood (viral load) was not different from that in placebo users who also became infected. Furthermore taking Truvada after HIV infection occurred did not:

- delay the detection of HIV’s genetic material in the blood
- delay the production and detection of HIV antibodies in the blood
- increase CD4+ cell counts or provide other benefit in people who became infected with this virus.

Results—HIV drug resistance

Some researchers are concerned that people who take Truvada and then become infected with HIV may develop resistance to the components of Truvada (tenofovir and FTC) and possibly other similar anti-HIV drugs (cross-

resistance). This would reduce their future treatment options.

No one who was uninfected *at the start of* the study and who became infected with HIV while taking Truvada showed evidence of drug resistance.

However, using sensitive HIV RNA tests, it was discovered that 10 participants who seroconverted during the course of the study were in fact infected at the start of the study, but did not test positive with the HIV rapid test used at screening. Two of these participants were in the group taking Truvada and both showed evidence of resistance to FTC—one of the drug components of Truvada. At least one of these cases of drug resistance resulted from being exposed to Truvada during acute HIV infection.

This result underscores the fact that PrEP should not be started in people with HIV infection. In addition to HIV antibody testing, other methods of screening for acute HIV infection are important to ensure that HIV is not present when PrEP is started.

Results—STIs

More than 1,000 of the 2,499 study participants were diagnosed with syphilis. STIs, such as syphilis, can increase the transmission of HIV by causing inflammation, sores or lesions in delicate ano-genital tissue. There was no evidence that Truvada prevented the transmission of STIs.

Results—Adherence

Taking medicines every day as directed is called adherence. This behaviour was also an important factor in the iPrEx study.

According to reports from participants, their overall adherence was high (around 90%). However, researchers found, in a small sub-group of participants assigned to receive Truvada, that only half had detectable levels of the drugs in their blood. This suggests that fewer adhered to their pill-taking schedule than reported.

Participants who were more adherent to PrEP were less susceptible to HIV infection. For those participants who reported taking PrEP at least 90% of the time, there was a 73% reduction in the relative risk of HIV infection.

Researchers also conducted blood tests on a selected sub-group of participants to assess levels of anti-HIV drugs. Based on these blood tests, researchers found there was a 92% reduction in HIV risk among people taking Truvada who had detectable drug levels compared with those who had undetectable drug levels. While this is encouraging, it is important to note that participants were offered a comprehensive prevention program, including safer sex counselling and condom distribution. Because the blood test analysis was not randomized, it is possible that the reduced infection rate was partly a result of greater adherence to the *entire prevention program* , and not only Truvada. For example, people who were more likely to adhere to Truvada may also have been more likely to use condoms.

Results—Side effects

Truvada is commonly used as part of combination therapy for HIV-positive people. When taken to *treat* HIV, Truvada is generally well-tolerated but can cause nausea, headache, vomiting and diarrhea in some users, at least initially. Also, reports have emerged linking tenofovir (one of the drugs in Truvada) to kidney dysfunction and thinning bones.

In the iPrEx study, participants taking Truvada were more likely to experience nausea compared with those taking a placebo.

- Truvada—22 cases of nausea
- placebo—10 cases of nausea

The nausea usually resolved within a few weeks and no one stopped treatment as a result of this symptom.

Some study participants also experienced unintentional weight loss (of 5% or more of their body weight), which occurred as follows:

- Truvada—34 cases of weight loss
- placebo—19 cases of weight loss

These differences in nausea and weight loss between Truvada and placebo recipients were statistically significant.

Temporary kidney dysfunction was detected in about 2% of Truvada users and 1% of placebo users. This problem resolved when people stopped taking Truvada. Seven Truvada users and three placebo recipients experienced kidney dysfunction so severe that they had to stop taking the study medications.

Results—Comprehensive prevention

The iPrEx study involved providing a comprehensive prevention program to high risk MSM, many of whom did not previously have access to such services. Risk reduction counseling was provided at each visit, screening and treatment for STIs was provided and approximately 500,000 condoms were distributed. Overall, researchers found a significant increase in condom usage and a significant decrease in the number of sex partners.

Caution and concerns in Canada and other high-income countries

The results of the iPrEx study show that when used for about one year, Truvada can provide partial protection against HIV infection, at least among high-risk MSM. However, before embarking on widespread use of Truvada there are several issues to consider.

1. Condoms still needed

Truvada is only modestly effective in preventing HIV infection and cannot replace safer sex. According to Dr. Kevin Fenton, Director of the National Center for HIV/AIDS at the American Centers for Disease Control and Prevention (CDC), while the iPrEx data are “encouraging, this is not the time for gay men to throw away their condoms.”

2. Resistance and reduced treatment options

PrEP use requires frequent HIV testing. It is very important that people considering PrEP are not infected with HIV because of the risk of developing drug resistance. More than 25% of people living with HIV in Canada are not aware of their HIV status. Furthermore, the risk of resistance may be greatest during acute HIV infection when conventional HIV tests will not detect infection.

3. Effectiveness of PrEP in other populations

The iPrEx study involved MSM who were at high risk for HIV infection. The primary mode of exposure to HIV was through rectal tissue during unprotected receptive anal intercourse. According to the investigators, this study does not provide any information about effectiveness or safety of PrEP for vaginal, penile or intravenous exposure to HIV. Further studies are needed to determine if PrEP has any effect in reducing HIV transmission from heterosexual vaginal sex, intravenous drug use or insertive anal sex.

4. Safety and use in the real world

We don’t know how willing gay and bisexual men will be to take PrEP over the long term. Even in people living with HIV, taking anti-HIV drugs on a regular basis is a challenge and can lead to long-term side effects that are difficult to manage. Truvada can affect the health of the kidneys and bones in HIV-positive people. Commonly used over-the-counter drugs such as acetaminophen (Tylenol) and ibuprofen (Advil, Motrin) can also affect kidney health.

PrEP must be provided within the context of a comprehensive prevention program. The iPrEx trial participants were frequently monitored for STIs, HIV and toxicity. They were also offered regular HIV risk counseling and adherence support. In the “real” world outside the clinical trial, for PrEP to work, people on PrEP will need close medical supervision, regular safer-sex counselling, and frequent testing for HIV and STIs. Some HIV-negative men may feel this level of bio-medical intervention is too intrusive.

5. PrEP and risk behaviour

Another concern is that some people may feel a false sense of security when using PrEP and decide to engage in more risky activities. If people using PrEP decide to have sex with more partners, use condoms less often, or share needles more frequently, then their overall risk for HIV infection (and other STIs) may increase because PrEP does not provide complete protection.

6. Cost

Currently, PrEP is a very expensive intervention. A month's supply of 30 Truvada pills costs at least $800 in Canada or the U.S.—$27 per day.

7. Unsupervised use of PrEP

PrEP involves taking anti-HIV drugs. These medications must be prescribed and monitored by a doctor, who can provide them in a safe and informed way. Some people may be tempted to experiment with drugs obtained from other sources—from a friend, people at parties, or over the internet. This could be harmful. Incorrect use of anti-HIV drugs can cause HIV drug resistance. It might also cause serious, even life-threatening, reactions in some people. Anti-HIV drugs can interact with other prescription drugs, recreational drugs and other substances. These interactions can be harmful, even when there are no symptoms.

PrEP resources:

CATIE Fact Sheet on "Pre-exposure prophylaxis (PrEP)" is available at:
http://www.catie.ca/en/fact-sheets/prevention/pre-exposure-prophylaxis-prep

CDC Statement on Results of iPrEx Trial:
www.cdc.gov/nchhstp/newsroom/iPrExMediaStatement.html

CATIE Fact Sheet on Truvada is available at:
http://www.catie.ca/en/fact-sheets/co-formulations/truvada

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—Sean R. Hosein

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