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A case of HIV transmission on PrEP and its implications

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At the 2016 Conference on Retroviruses and Opportunistic Infections (CROI), David Knox, MD, presented information about a case of HIV transmission in a man who had multiple sexual partners and who did not use condoms—and who was taking pre-exposure prophylaxis (PrEP) in the form of daily Truvada.

In this *CATIE News* bulletin we review key details about this important case and its possible implications for HIV risk reduction in the future. For people at high risk for HIV infection who are considering initiating Truvada as PrEP to help reduce their risk, and for those currently taking PrEP, we present advice from doctors who are experienced with the use of Truvada as PrEP.

Although this is the first *well-documented* case of HIV transmission in someone who is highly adherent to Truvada as PrEP, it is not the first case of such a transmission. Therefore, for people using or considering initiating medicines to reduce their risk of acquiring HIV via sexual transmission, it is important to bear in the mind the points listed below.

Truvada—which contains two anti-HIV drugs, tenofovir + FTC (emtricitabine)—has helped reduce the risk of HIV infection in thousands of people. Risk reduction is greatest when Truvada is used exactly as directed—as part of a package of measures that include the following:

- screening for HIV and sexually transmitted infections (STIs) prior to initiating Truvada
- treating any STIs that are detected
- getting vaccinated against hepatitis B (if necessary), and potentially hepatitis A and human papillomavirus
- the correct and consistent use of condoms
- regular and frequent testing (at least every three months) for HIV and testing, and treatment if necessary, for other STIs

Case details

A Toronto man in his early 40s who had tested negative for HIV and common STIs (syphilis, gonorrhoea and chlamydia) sought Truvada as PrEP from his doctor in the spring of 2013. After assessment, blood tests and counselling, the man began taking Truvada every day exactly as directed. For the next two years he continued to be highly adherent and his screening for HIV was repeatedly negative.

In April 2015 the man complained of persistent and severe abdominal pain. As this was an issue that could be potentially serious, he was referred to the Emergency Room of a local hospital. Initially doctors did not suspect acute HIV infection because the patient said that he took Truvada every day exactly as directed. After a series of tests ruled out inflammatory bowel disease, in early May 2015 the man's doctor had his blood tested for HIV antibodies and an HIV protein called p24 antigen. The man tested positive for p24 antigen but negative for HIV antibodies, which is consistent with early HIV infection.

Fearing the possibility that his patient was undergoing very early HIV infection, Dr. Knox prescribed anti-HIV therapy as follows:

- the protease inhibitor darunavir (Prezista)
- a small dose of the protease inhibitor ritonavir (Norvir), which raises and prolongs the level of darunavir in the

body

- the integrase inhibitor raltegravir (Isentress)

Truvada was continued, as this drug could have potentially provided additional antiviral activity when combined with the other drugs.

Confirming adherence

The man's doctor knew that it was important to assess the patient's adherence to Truvada. So, with the limited blood samples available to him (the vast majority of family doctors do not have the high-level facilities to store blood and other fluid samples that are standard in research labs), he had a tiny portion of these samples undergo sophisticated analysis in a research laboratory in Vancouver under the supervision of virologist Richard Harrigan, PhD, at the BC Centre for Excellence in HIV/AIDS. Specifically, these analyses assessed the levels of the drugs that are in Truvada—tenofovir and FTC.

Another way of assessing adherence, though less direct, is to check pharmacy records of when the patient refilled his prescriptions. In large analyses done in B.C., timely re-filling of prescriptions has been found to be highly associated with good adherence (and good clinical outcomes) among people who take anti-HIV medicines.

The analyses of the patient's blood taken from early May 2015 were similar to what has been done in some large clinical trials in which Truvada was used as PrEP. Researchers in B.C. found that the levels of tenofovir in the patient's blood were very high and indicated that he had been adherent to Truvada for a long time. Other, more sophisticated tests (mass spectrometry) confirmed that the patient's blood contained very high levels of tenofovir and FTC. Thus, there is no doubt that the patient was taking Truvada for quite some time, exactly as directed.

Focus on the strain of HIV

Prior to these blood tests that sought to assess the patient's adherence, the man had *not* taken other anti-HIV medicines apart from Truvada. However, genetic analysis of the virus with which he was now infected revealed a strain of HIV that was unusual—it had changes, or mutations, in its genetic makeup that allowed it to partially or wholly resist many treatments. Such mutations generally arise because medicines have not been taken exactly as directed.

Below we list by drug classes the treatments to which his strain of HIV could be resistant:

Nukes (nucleoside analogues)

- two-fold reduced susceptibility to abacavir (Ziagen)
- 1.3-fold reduced susceptibility to tenofovir (Viread and in Truvada)
- high-level resistance to 3TC (lamivudine)
- high-level resistance to FTC (in Truvada)

The specific mutation that confers resistance to 3TC and FTC is called M184V. We will discuss the significance of this mutation later in this bulletin.

Non-nukes

- resistance to nevirapine (Viramune)

Integrase inhibitors

- reduced susceptibility to raltegravir (Isentress)
- resistance to elvitegravir (in Genvoya and Stribild)

Furthermore, laboratory testing with cells infected with this strain of HIV and different concentrations of drugs confirmed the genetic analysis.

Treatment

The amount of HIV in the man's blood was relatively low: 28,000 copies/mL in early May 2015.

Four weeks after blood tests first suggested HIV infection and about three weeks after initiation of treatment, his viral load fell to less than 50 copies/mL. Once this occurred, given the genetic and other analyses of resistance, and to avoid the possibility of HIV becoming resistant to the drugs he was currently taking, Dr. Knox changed the man's treatment to the following combination:

- dolutegravir (Tivicay)
- darunavir + cobicistat (this latter drug raises and maintains levels of darunavir in the body; both drugs are sold in one pill called Prezcoibix)
- rilpivirine (Edurant)

Thus, due to the strain of multidrug-resistant HIV (MDR-HIV) with which he was infected, the man was placed on a complex regimen of anti-HIV drugs. Such regimens are usually associated with side effects, yet Knox told us that these drugs were "remarkably well tolerated" by his patient.

Mutations and their discontents

The cluster of mutations present in the man's strain of MDR-HIV are unusual and suggest that the person who transmitted this strain had been exposed to older anti-HIV drugs in the past that are not commonly used today in routine HIV care in Canada and other high-income countries. These older drugs included the following:

- AZT (zidovudine, Retrovir)
- d4T (stavudine, Zerit)
- nevirapine (Viramune)

However, the virus also had resistance to the integrase inhibitor elvitegravir; this drug only came into use in Canada and other high-income countries in about 2012.

This cluster of mutations in the man's virus is rare. Dr. Harrigan estimates that less than 1% of HIV-positive Canadians who have a persistently detectable viral load have such a strain.

However, there are other aspects of this case and drug-resistant mutations that are concerning, and we explore those next.

The peculiar impact of M184V

A mutation in HIV called M184V allows the virus to resist the effects of the drugs 3TC and FTC (one of the drugs found inside Truvada). However, M184V has other effects on HIV—it can make it susceptible to the antiviral activity of tenofovir. In the specific case described here, the presence of additional mutations associated with prior treatment failure with the drugs AZT and/or d4T may have contributed to resistance against both FTC and tenofovir.

Dr. Harrigan's lab is involved in screening tens of thousands of blood samples from HIV-positive Canadians for possible resistance to treatment. Based on the data that his lab has accumulated over the many years of doing this work, Dr. Harrigan estimates that about 10% of HIV-positive Canadians who have a persistently detectable viral load have HIV with the M184V mutation.

If people using Truvada as PrEP encounter a virus with M184V *and* additional resistance mutations such as the ones reported in this particular case, Truvada may not always be able to provide its full antiviral effect against this strain of HIV. Thus, it is possible that, in the future, additional cases of HIV infection could occur even in highly adherent Truvada users who do not use condoms.

The 10% estimate for the overall presence of strains of HIV with the M184V mutation is an average; it does not mean that there is a 10% risk of someone encountering this virus in Canada.

Mutations and the context of risk

For a person using Truvada, the real risk of encountering HIV that is partially or wholly resistant to the drugs inside Truvada depends on one's sexual network. Some sexual networks are small, such as those restricted to a monogamous couple. Others may be larger, such as in cases where some couples occasionally have a threesome.

Some people have even larger sexual networks, such as those with many anonymous sexual encounters. Since everyone's sexual network is different, their risk for potential exposure to partially or wholly drug-resistant virus will be different, depending on the relative concentration of such viruses within their sexual network.

Advice for people who are using or considering Truvada as PrEP

Here are some wise words from two experienced doctors who have counselled many patients about reducing their risk for HIV and how best to use Truvada:

David Knox, MD:

“If your goal is to remain HIV negative, then use Truvada every day and condoms as often as possible.”

Paul MacPherson, MD, PhD:

“There are no randomized controlled studies specifically comparing the impact of barebacking to barebacking with Truvada on the risk of becoming infected with HIV. Therefore, the efficacy of Truvada alone in reducing the risk of HIV transmission is not known. The data from PrEP studies tell us that combination risk reduction—taking Truvada every day and using condoms regularly—is highly effective. Driving our car can be a pleasurable experience. However, we still buckle our seat belts, stop for red lights and count on the airbag to deploy if we are in a collision. Do the same for sex. Enjoy it but take Truvada every day and use a condom.”

Bear in mind

Truvada has helped to reduce the risk of HIV infection in thousands of people and *will continue to do so in the future*. Dr. Knox notes that Truvada as PrEP is “imperfect,” which is why the simultaneous use of condoms is important—they provide an added layer of protection from HIV and some STIs.

Transmission of drug-resistant HIV to Truvada users is rare.

We are very lucky that Dr. Knox and his colleagues had rapid access to a vast, talented and knowledgeable network of physicians and scientists who were willing to advise and help them. The average family doctor does not usually have access to such a network, proper storage facilities for blood and other biological samples, or the time in which to engage in the painstaking task of evaluating and documenting the case of transmission in question. The latter is not something for which physicians are reimbursed by health authorities. Indeed, when not caring for his patients, Dr. Knox has spent many long weekends engaged in the work of documenting this case.

The present case should be seen as the first *well-documented* case of HIV transmission in a person who is highly adherent to Truvada as PrEP and who did not use condoms. Indeed, the Canadian prescribing information for Truvada as PrEP makes clear that other cases of transmission have occurred in Truvada users and that Truvada alone cannot be relied upon to eliminate the risk of sexual transmission of HIV.

Resources

[Truvada approved for HIV prevention in Canada](#) - CATIE News

[Truvada](#) - CATIE fact sheet

[Pre-exposure prophylaxis \(PrEP\)](#) - CATIE fact sheet

[CATIE statement on the use of pre-exposure prophylaxis \(PrEP\) to prevent the sexual transmission of HIV](#)

[Condoms, PrEP, and the use of antiretroviral treatment to prevent HIV](#) - CATIE webinar

[PrEP for the prevention of HIV infection in the United States: A clinical practice guideline](#) ^{PDF} - US Centers for Disease Control and Prevention (CDC)

[Clinical providers' supplement for providing PrEP](#) ^{PDF} - CDC

[Interim guidance on providing HIV PrEP](#) ^{PDF} - Quebec Ministry of Health (French only)

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—Sean R. Hosein

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