CATIE Canada's source for HIV and hepatitis C information
La source canadienne de renseignements sur le VIH et l'hépatite C

CATIE-News

CATIE's bite-sized HIV and hepatitis C news bulletins.

A case of HIV transmission on PrEP and its implications

15 March 2016

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, gonorrhea 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 Prezcobix)
- 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 – US Centers for Disease Control and Prevention (CDC)

Clinical providers' supplement for providing PrEP – CDC

Interim guidance on providing HIV PrEP – Quebec Ministry of Health (French only)

Pre-exposure prophylaxis (PrEP) guidelines – B.C. Centre for Excellence in HIV/AIDS

Acknowledgements

We thank the following doctors and virologists for their helpful discussions, research assistance and expert review:

- David Knox, MD – Maple Leaf Medical Clinic, Toronto
- Paul MacPherson, MD, PhD – Ottawa Hospital Research Institute
- Richard Harrigan, PhD – BC Centre for Excellence in HIV/AIDS, Vancouver
- Thibault Mesplèd, PhD – Wainberg Laboratory, McGill University, Montreal

—Sean R. Hosein

REFERENCES:

1. Gilead Sciences. Health Canada issues notice of compliance for Gilead's Truvada for reducing the risk of sexually acquired HIV infection. *Press release* . 29 February 2016.
2. Gilead Sciences. Truvada (emtricitabine/tenofovir disoproxil fumarate tablets). *Product monograph* . 23 February 2016.
3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *New England Journal of Medicine* . 2010 Dec 30;363(27):2587-99.
4. Knox DC, Tan DH, Harrigan PR, et al. HIV infection with multi-class resistance despite pre-exposure prophylaxis (PrEP). *Conference on Retroviruses and Opportunistic Infections (CROI)* , 22-25 February 2016. Abstract 169aLB.
5. Hammer T, Nielsen KR, Munkholm P, et al. The Faroese IBD study – Incidence of Inflammatory Bowel Diseases across 54 years of population-based data. *Journal of Crohn's & Colitis* . 2016; *in press* .
6. Zhulina Y, Udumyan R, Tysk C, et al. The changing face of Crohn's disease: a population-based study of the natural history of Crohn's disease in Örebro, Sweden 1963-2005. *Scandinavian Journal of Gastroenterology* . 2016 Mar;51(3):304-13.
7. Peters PJ, Westheimer E, Cohen S, et al. Screening yield of HIV antigen/antibody combination and pooled HIV RNA testing for acute HIV infection in a high-prevalence population. *Journal of the American Medical Association*. 2016 Feb 16;315(7):682-90.
8. Gross R, Yip B, Lo Re V 3rd, et al. A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression. *Journal of Infectious Diseases* . 2006 Oct 15;194(8):1108-14.
9. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Science Translational Medicine* . 2012 Sep 12;4(151):151ra125.
10. Hendrix CW, Andrade A, Bumpus NN, et al. Dose frequency ranging pharmacokinetic study of tenofovir-emtricitabine after directly observed dosing in healthy volunteers to establish adherence benchmarks (HPTN 066). *AIDS Research and Human Retroviruses* . 2016 Jan;32(1):32-43.
11. Gandhi M, Glidden DV, Liu A, et al. Strong correlation between concentrations of tenofovir (TFV) emtricitabine (FTC) in hair and TFV diphosphate and FTC triphosphate in dried blood spots in the iPrEx Open Label Extension: implications for pre-exposure prophylaxis adherence monitoring. *Journal of Infectious Diseases* . 2015 Nov 1;212(9):1402-6.
12. Hoenigl M, Green N, Camacho M, et al. Signs or symptoms of acute HIV Infection in a cohort undergoing community-based screening. *Emerging Infectious Diseases* . 2016 Feb;22(3).
13. Wainberg MA. The impact of the M184V substitution on drug resistance and viral fitness. *Expert Review of Anti-Infective Therapy* . 2004 Feb;2(1):147-51.
14. Fox J, Brady M, Alexander H, et al. Tenofovir disoproxil fumarate fails to prevent HIV acquisition or the establishment of a viral reservoir: two case reports. *Infectious Diseases and Therapy* . 2016; *in press* .
15. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. *Lancet Infectious Diseases* . 2014 Nov;14(11):1055-64.
16. Mayer KH, Krakower DS, Boswell SL. Antiretroviral preexposure prophylaxis: opportunities and challenges for primary care physicians. *Journal of the American Medical Association* . 2016 Mar 1;315(9):867-8.

Produced By:

555 Richmond Street West, Suite 505, Box 1104
Toronto, Ontario M5V 3B1 Canada
Phone: 416.203.7122
Toll-free: 1.800.263.1638
Fax: 416.203.8284
www.catie.ca
Charitable registration number: 13225 8740 RR

Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

CATIE provides information resources to help people living with HIV and/or hepatitis C who wish to manage their own health care in partnership with their care providers. Information accessed through or published or provided by CATIE, however, is not to be considered medical advice. We do not recommend or advocate particular treatments and we urge users to consult as broad a range of sources as possible. We strongly urge users to consult with a qualified medical practitioner prior to undertaking any decision, use or action of a medical nature.

CATIE endeavours to provide the most up-to-date and accurate information at the time of publication. However, information changes and users are encouraged to ensure they have the most current information. Users relying solely on this information do so entirely at their own risk. Neither CATIE nor any of its partners or funders, nor any of their employees, directors, officers or volunteers may be held liable for damages of any kind that may result from the use or misuse of any such information. Any opinions expressed herein or in any article or publication accessed or published or provided by CATIE may not reflect the policies or opinions of CATIE or any partners or funders.

Information on safer drug use is presented as a public health service to help people make healthier choices to reduce the spread of HIV, viral hepatitis and other infections. It is not intended to encourage or promote the use or possession of illegal drugs.

Permission to Reproduce

Production of this content has been made possible through a financial contribution from the Public Health Agency of Canada.

Available online at:
http://www.catie.ca/en/catienews/2016-03-15/case-hiv-transmission-prep-and-its-implications