DALHOUSIE UNIVERSITY FACULTY OF MEDICINE **Guideline for HIV and Related Illness Prevention (including for International Electives)**	**Responsible unit:** Undergraduate Medical Education Office	**Established:** February 2012 **Last revised:** August 2023

A. Background & Purpose

Dalhousie University has a responsibility to provide advice and assistance to students undertaking foreign electives. Students also have a responsibility to themselves when studying in foreign countries, where certain infections may be encountered more frequently than in Canada. This document provides guidance for students undertaking Global Health Electives in the Faculty of Medicine, so that they can protect themselves from infection with HIV (Human Immunodeficiency Viruses), which is common in many parts of the world. This document is a guide, and not a definitive statement on occupational HIV prevention. The document addresses HIV prevention from a clinical standpoint only, assuming that students are aware of the need for protection in personal situations. In particular, the document provides advice that is easy to understand and follow, so that students will be able to make decisions that do not require the weighing of a very large number of probabilities in difficult situations.

The guideline has one underlying principle: proactive thought. It is expected that students who undertake foreign electives will have seriously considered the steps they will take if an exposure or possible exposure to HIV occurs, including wound management, chemoprophylaxis and repatriation to Canada or transfer to another developed country. This will involve developing a knowledge of i) the prevalence of HIV infection in the country to be visited; and ii) the types of duties and experiences the student will have during the elective (exposure to potentially infected blood/body fluids during surgical, medical, and obstetrical procedures). The student should also develop a plan for action if a potential exposure does occur, prior to departure for the elective experience.

The document will address five main areas: 1. the epidemiology of HIV infection; 2. prevention of exposure; 3. acute exposure management; 4. risk assessment after exposure in the clinical situation; 5. post-exposure prophylaxis; 6. considerations to be made prior to travel.

B. Application

Dalhousie students planning international electives will review plans with the Faculty of Medicine's Office of Community Partnerships and Global Health, including review of this guidance document. Students are then obliged to review their travel health needs, including HIV prevention precautions with their care provider/travel clinic in advance of travel to ensure appropriate prescriptions are provided.

C. Definitions

- HBV: Hepatitis B
- HCV: Hepatitis C
- HIV: HIV and AIDS (who.int)

- Office of Community Partnerships and Global Health: Global Health Office – Dalhousie University

- UGME: Undergraduate Medical Education Faculty of Medicine

- Student Affairs: The office of Student Affairs Faculty of Medicine

D. Guideline

1. EPIDEMIOLOGY OF HIV INFECTION

(i)International Statistics. According to the World Health Organization (1), as of 2021, 38.4 million people worldwide were estimated to be living with HIV/AIDS. More than 95% of those with HIV/AIDS are adults and 67% live in sub-Saharan Africa, where on average 5% of adults (or, 50/1000) have HIV infection. Elsewhere in the world, from 1-9 people/1000 have HIV infection.

Additionally, more than 95% of all HIV-infected people now live in the developing world, which has experienced 95% of all deaths from AIDS. (2)

(ii) Prevalence Rates by Individual Country. To understand the risk of HIV infection due to occupational exposure in various settings, it is necessary to have some estimate of the prevalence of infection in the country to be visited, which can be very high, especially sub-Saharan Africa. While it is not possible to list estimates of infection for all areas of all countries, the UNAIDS website: "UNAIDS/WHO/ UNICEF Epidemiological fact sheets on HIV and AIDS" (3) provides very useful information on a country-specific basis. This site also gives demographic information that could prove useful to students for planning their elective experiences.

(iii) HIV Infection Due to Occupational Exposure in the United States. The literature suggests that accidental blood exposures are common among health care workers, including medical students and residents. One study in France reported that at least half of residents answering the questionnaire had experienced an accidental blood exposure; with approximately half occurring during a surgical procedure. (4) In another study, 34% of European medical students reported at least one needle stick injury during medical school, with 34% not reporting the injury to occupational health or their supervisor. (5) In a recent systematic review and meta-analysis, the pooled prevalence of needlestick injuries over a career and in the last year was 56.2% and 32.4%, respectively. (6)

Data from the U.S. provides some indication of the risk of contracting HIV through occupational exposure. Of U.S. healthcare workers whose investigations were completed from 1985-2013, 57 had documented seroconversion to HIV following occupational exposures. The routes of exposure which

resulted in infection were: 49 percutaneous (punctures/cuts); 5 mucocutaneous (mucous membrane and/or skin); 2 both percutaneous and mucocutaneous; and 2 which were unknown. Forty-nine healthcare workers were exposed to infected blood; 4 to the virus in a laboratory; 1 to bodily fluid; 4 to a fluid which was not specified. One hundred and fifty possible cases of HIV infection have been reported in healthcare personnel. The most recent possible new case of occupationally-acquired HIV reported to CDC was in 2009, and no new documented cases have been reported since 1999. (7)

The risk of seroconversion from occupational exposure to HIV is small, but measurable. The estimated risk of transmission following accidental exposure to contaminated blood (defined as any contact with blood or a body fluid contaminated by blood as a result of injury with a needle or any other sharp instrument) , or via mucous membrane or an existing cutaneous condition (e.g., eczema) is 0.3% per percutaneous exposure and 0.009% per mucocutaneous exposure.(8) The most common procedures that present a risk of contaminated blood exposure to individuals carrying out clinical duties are:

- Taking blood samples and samples of body fluids containing blood (9)
- Surgical interventions, especially those of long duration and where excessive bleeding may occur (9)
- The cleaning of reusable medical material (8)
- (iv) Occupational Health Considerations in Resource Poor Countries. It is speculated that medical students undertaking electives in foreign countries may be at higher risk of injury—- in part due to participating in procedures they have little experience doing in their home programs. In a study of University of Pennsylvania students doing electives in Botswana, 25% of them reported a blood or body fluid exposure, almost equally divided between needle sticks (50% involved poor handling of sharps and bodily fluids) and splashes, almost all occurring during phlebotomy and intravenous line placement. (10)

Several other reasons are suggested for an increased risk of accidental occupational exposure to blood borne viruses in the developing world. (11) These include a higher prevalence of blood borne virus infection in many of these countries; greater disease severity among those infected; use of hazardous equipment and procedures; a greater number of informal health care workers; and a culture of using injections rather than other medication delivery methods.

2. PREVENTION OF EXPOSURE

The best HIV prevention is preventing exposure to the virus in the first place. Be vigilant in using safe sharps practices:

- Do not recap needles
- Do not manipulate needles by hand
- Dispose of sharps safely
- Do not do an invasive procedure that you do not feel safe doing
- Do not pass sharps hand-to-hand
- Use blunt needles or needleless devices whenever available
- Protect your mouth and eyes
- Wear mask and goggles or other facial protection whenever splashes, or sprays may happen during any procedure

3. MANAGEMENT OF ACUTE EXPOSURE

In cases of injury by blood-contaminated medical equipment, or when contact occurs between broken skin and body fluids:

- Allow wound to bleed freely and wash wound or exposed skin area with soap and water for 10 minutes, rinsing frequently
- After exposure affecting eyes or mucous membranes: rinse the exposed area for 10 minutes with isotonic saline solution (if not available use clean water)

4. RISK ASSESSMENT AFTER EXPOSURE IN THE CLINICAL SITUATION

Students should contact their travel health insurance provider (Backpack Insurance) as soon as possible after an exposure to help coordinate care and ensure coverage. Please see section E for details on insurance for international electives.

The risk of occupational infection with HIV depends on several factors:

- The type of incident. Incidents involving large bore needles with visible contamination, and those involving IV or arterial line needles pose a higher risk of infection.
- The degree of exposure. Deep wounds constitute a large exposure, needle pricks moderate exposure, and superficial dermal erosions, minimal exposure.
- HIV, HBV, HCV status of the source, as assessed by health status. This is often the most difficult area of risk assessment and is usually due to lack of testing resources. If testing is available, it should be done with the patient's informed consent, or as dictated by local policies and regulations. Whether or not testing can be carried out, the source can usually be questioned about risk activities and health status to determine likelihood of HIV, Hepatitis B, Hepatitis C infection and likely degree of infectiousness.

If the source is not available, risk assessment will depend upon the type of exposure, and to a certain extent, knowledge of country/regional HIV, Hepatitis B and C epidemiology.

5. DECISIONS ABOUT CHEMOPROPHYLAXIS

The administration of antiretroviral drugs as postexposure prophylaxis (PEP) for HIV should be considered after significant exposure to infected or potentially infected blood or body fluids. This decision is made considering local epidemiology, nature of the exposure and risk status of the source. PEP has been shown to be safe and associated with decreased risk for occupationally-related HIV infection. As a guide to thinking about such decisions, the following extract from the U.S. Public Health Service Guidelines11 is offered: The use of PEP for occupational exposure to HIV is either recommended, considered, or not offered depending on the circumstances of the exposure and the characteristics of the source. (8)(12) (See Tables 1 and 2).

TABLE 1. Recommended HIV postexposure prophylaxis (PEP) for percutaneous injuries

Exposure type	Infection status of source: HIV-positive, class 1*	HIV-positive, class 2*	Source of unknown HIV status†	Unknown source§	HIV-negative
Less severe¶	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely	No PEP warranted
More severe§§	Recommend expanded 3-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP** for source with HIV risk factors††	Generally, no PEP warranted; however, consider basic 2-drug PEP** in settings in which exposure to HIV-infected persons is likely	No PEP warranted

* HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, acquired immunodeficiency syndrome, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

† For example, deceased source person with no samples available for HIV testing.

§ For example, a needle from a sharps disposal container.

¶ For example, solid needle or superficial injury.

** The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

†† If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.

§§ For example, large-bore hollow needle, deep puncture, visible blood on device, or needle used in patient's artery or vein.

TABLE 2. Recommended HIV postexposure prophylaxis (PEP) for mucous membrane exposures and nonintact skin* exposures

Exposure type	Infection status of source: HIV-positive, class 1†	HIV-positive, class 2†	Source of unknown HIV status§	Unknown source¶	HIV-negative
Small volume**	Consider basic 2-drug PEP††	Recommend basic 2-drug PEP	Generally, no PEP warranted§§	Generally, no PEP warranted	No PEP warranted
Large volume¶¶	Recommend basic 2-drug PEP	Recommend expanded ≥3-drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP†† for source with HIV risk factors§§	Generally, no PEP warranted; however, consider basic 2-drug PEP†† in settings in which exposure to HIV-infected persons is likely	No PEP warranted

* For skin exposures, follow-up is indicated only if evidence exists of compromised skin integrity (e.g., dermatitis, abrasion, or open wound).

† HIV-positive, class 1 — asymptomatic HIV infection or known low viral load (e.g., <1,500 ribonucleic acid copies/mL). HIV-positive, class 2 — symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load. If drug resistance is a concern, obtain expert consultation. Initiation of PEP should not be delayed pending expert consultation, and, because expert consultation alone cannot substitute for face-to-face counseling, resources should be available to provide immediate evaluation and follow-up care for all exposures.

§ For example, deceased source person with no samples available for HIV testing.

¶ For example, splash from inappropriately disposed blood.

** For example, a few drops.

†† The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the treating clinician regarding the risks versus benefits of PEP.

§§ If PEP is offered and administered and the source is later determined to be HIV-negative, PEP should be discontinued.

¶¶ For example, a major blood splash.

In situations where the HIV status of the source is not immediately known, the decision to initiate PEP should be made on a case-by-case basis and may be modified if additional information becomes available. If a decision is made to take prophylactic therapy, the following is recommended:

Treatment is by combination therapy and if it is initiated, it is assumed that the student will return to Canada or go to another developed country for further consultation within one week. For exposures

deemed to be significant as per the guidelines, treatment is initiated as soon as possible after exposure with a 5-day starter kit using the following protocol:

Raltegravir 400mg po bid
PLUS
Truvada 1tab po daily
(Tenofovir + Emtricitabine)

The choice of prophylaxis may vary if there is reason to believe that the source is infected with an antiviral resistant strain of HIV. Therefore, detailed evaluation of the injury and source and review with an expert consultant is necessary. A two-drug regimen represents the basic one with a third drug added for high-risk exposure only (see above tables). Reassessment should take place to determine follow up testing recommendations and if a further 23 days of medication is required.

Please see Appendix 1 (Truvada information), Appendix 2 (Raltegravir information).

6. CONSIDERATIONS PRIOR TO TRAVEL

Reviewing travel health insurance policy prior to travel is essential for students to be familiar with contact information and procedures if care is required. Please see Section E. Procedures, for details on insurance for international electives.
Students should be certain that they understand several issues about occupational HIV exposure before leaving for their electives. These include:

- Being aware of the risks of occupational exposure, the prevalence of HIV in the country in which the elective is being carried out, the types of procedures and interventions they are likely to take part in during the elective, and how to minimize risk of occupational exposures.
- Having an up-to-date combination PEP starter therapy kit either with them personally or being certain that combination therapy is readily accessible at the elective site. Being familiar enough with travel arrangements in the elective country so that expedient (i.e., within one week) travel to Canada or another developed country can be arranged.
- Giving due pre-consideration of various scenarios of possible exposure, so that decisions can be made reasonably quickly and well. Discussion with the Dalhousie supervisor or another qualified faculty member is recommended prior to travel.

E. Procedures

The Office of Community Partnerships and Global Health:

Dalhousie students planning international electives are required to have their elective plans reviewed and approved by the Office of Community Partnerships and Global Health. Students are required to review relevant policies, including this guidance document on HIV, and the International Travel Policy for Dalhousie students (InternationalTravelPolicy-Feb 2019.pdf (dal.ca)).

Students in contact with the Office of Community Partnerships and Global Health with questions on acute exposures to HIV, HBV, HCV and any related illnesses will be guided to Backpack Insurance for review of acute situations and further direction while away.

Students are required to obtain travel and health insurance that meets Dalhousie requirements. Current policy requires students to obtain Backpack Insurance through Student VIP. In the case of an HIV, HBV, HCV and related illness exposure, students should contact Backpack insurance as soon as possible as they can provide advice and help with care coordination.

All Dalhousie students also have access to International SOS which provides 24/7 access to emergency travel assistance and provides safety reports to travellers, including health safety advice which students should review prior to travel.

Students are required to visit a travel health professional as part of their predeparture preparations before an international elective. During that consultation, students should obtain all necessary prescriptions and immunizations and should discuss the potential need for HIV prophylaxis.

Student Affairs:

Students are advised to contact Student Affairs to provide an update on any acute exposure or medical scenario while on international electives, and to follow up with Student Affairs on return from travel to review status and ensure that student and patient safety policies are adhered to.

F. Other

Records: All relevant student medical records will be kept confidentially at Student Affairs.

References:

(1) IN DANGER: UNAIDS Global AIDS Update 2022 | HIV/AIDS Data Hub for the Asia-Pacific Region
(2) https://www.unaids.org/en/resources/fact-sheet Global HIV & AIDS statistics — Fact sheet | UNAIDS
(3) Fact sheet - Latest global and regional statistics on the status of the AIDS epidemic. (unaids.org)
(4) Clinical Microbiology and Infection 2010; 17 (3) (published online)
(5) International Journal of Hygiene and Environmental Health 2011; 214:407-10
(6) Worldwide Prevalence of Occupational Exposure to Needle Stick Injury among Healthcare Workers: A Systematic Review and Meta-Analysis (hindawi.com)
(7) mm6353.pdf (cdc.gov)
(8) Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. (cdc.gov)
(9) Médicins Sans Frontières. Procedures to be Followed After an Accidental Exposure to Blood. MSF Medical Departments. July 1997
(10) Journal of General Internal Medicine 2010; 26:561-4
(11) Journal of Hospital Infection 2009; 72:285-91
(12) Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis. Morbidity and Mortality Weekly Report; September 30, 2005; 54 (RR-9).

Appendices:

(1) Truvada (Tenovir + Emtricitabine)
(2) Raltegravir

Truvada

FACT SHEET

Published
2019

Summary

Truvada is the name of a fixed-dose co-formulation of two anti-HIV drugs: tenofovir and FTC all in one pill. Truvada is used as part of combination therapy for people with HIV. Some doctors may also prescribe Truvada to HIV-negative people as part of a package of HIV prevention tools to help reduce the risk of HIV transmission. Truvada is generally well-tolerated. Common side effects of Truvada can include dizziness, headache, nausea and vomiting. Truvada is taken once-daily with or without food.

What is Truvada?

Truvada is the brand name of a fixed-dose co-formulation of two anti-HIV drugs: tenofovir (Viread) and FTC (emtricitabine) all in one pill. Generic formulations are also available.

How does Truvada work?

When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. To make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced the production of HIV slows.

The two medications inside Truvada are as follows:

- Tenofovir DF – this belongs to a group or class of drugs called nucleotide analogues ("nukes")
- FTC – this belongs to a group of drugs called nucleoside analogues ("nukes")

Both medicines inside Truvada interfere with an enzyme called reverse transcriptase, which is used by HIV-infected cells to make new viruses. Since Truvada reduces the activity of reverse transcriptase, it causes HIV-infected cells to slow down or stop producing new viruses.

Truvada, when taken as part of a package of HIV prevention tools (frequent screening for HIV and other sexually transmitted infections, safer sex counselling, use of condoms), can significantly reduce the risk of HIV transmission in some people. For more information about this, see CATIE's fact sheet *Oral pre-exposure prophylaxis (PrEP)*.

CONTACT US

by telephone
1-800-263-1638
416-203-7122

by fax
416-203-8284

by e-mail
info@catie.ca

by mail
555 Richmond Street West
Suite 505, Box 1104
Toronto ON M5V 3B1

CATIE
Canada's source for HIV and hepatitis C information

How do people with HIV use Truvada?

Truvada is taken in combination with other anti-HIV drugs including non-nukes (NNRTIs), protease inhibitors or integrase inhibitors. Such combinations are called antiretroviral therapy, or ART. For more information on ART, see CATIE's *Your Guide to HIV Treatment*.

Neither Truvada nor any other anti-HIV medication is a cure for HIV. It is therefore important that you see your doctor regularly so that he/she monitors your health.

Evidence shows that HIV-positive people who are on ART, engaged in care, and have an ongoing undetectable viral load are substantially less likely to transmit HIV to others, be it through sex, when sharing equipment to use drugs or during pregnancy and birth. In fact, the evidence for sexual transmission shows that people on ART who maintain an undetectable viral load do not pass HIV to their sexual partners. For further information see the CATIE fact sheet *HIV treatment and an undetectable viral load to prevent HIV transmission*. However, it is still a good idea to use condoms because they can reduce your risk for getting and passing on other sexually transmitted infections.

How do people who are HIV negative use Truvada as PrEP?

HIV-negative people can take Truvada to reduce their risk of becoming infected with HIV. People taking Truvada as PrEP as part of a package of HIV prevention tools should be tested for HIV and other sexually transmitted infections every three months and also receive safer sex and adherence counselling if needed. For healthcare professionals interested in prescribing Truvada as PrEP, see *Canadian guidelines on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis*.

Warnings

1. Lactic acidosis

Higher-than-normal levels of lactic acid can occur in the blood. This condition is called lactic acidosis and has happened in some HIV-positive people who have used tenofovir, FTC or related anti-HIV drugs. Women who are overweight are at increased risk for lactic acidosis. Sometimes the livers of people with lactic acidosis become swollen because of fatty deposits. Signs and symptoms of lactic acidosis may include the following:

- nausea
- vomiting
- abdominal pain
- diarrhea
- unexpected tiredness
- unexpected muscle pain
- feeling cold especially in the arms and legs
- feeling dizzy or light-headed

If these symptoms persist, see your doctor right away.

2. Hepatitis B

Truvada contains tenofovir and FTC. Both of these drugs have anti-hepatitis B virus (HBV) activity. People with an HBV infection who take Truvada and then later stop may experience worsening HBV infection (commonly called "flares"). People who are co-infected with HIV and hepatitis-causing viruses and who take ART are sometimes at increased risk for liver injury. It is important to have regular blood tests so that your doctor can assess the health of your liver.

If you have HBV infection, talk to your doctor before you start Truvada. If you are not sure if you have HBV, ask your doctor about getting tested. If you later need to change your therapy from Truvada, remind your doctor that you have HBV. If lab tests reveal that you do not have HBV, speak to your doctor about getting a vaccine to protect you from HBV.

3. Pancreatitis

Painfully swollen pancreas glands have been reported in some people taking tenofovir as part of ART. Higher-than-normal levels in the blood of the

enzyme amylase (made by the pancreas gland) have been detected in some people taking tenofovir. This increase may be suggestive of inflammation in the pancreas gland. Symptoms of pancreatitis can include the following:

- abdominal pain, particularly when laying down
- nausea
- vomiting
- unexpected sweating
- fever
- anxiety

If these symptoms occur, talk to your doctor right away.

4. Kidney injury

Tenofovir DF can cause kidney dysfunction and injury. If you or a close family member have kidney problems, tell your doctor. For more about tenofovir and the kidneys, please see the section on side effects later in this fact sheet.

Side effects

1. General side effects

Truvada is generally well-tolerated. In some cases, temporary side effects such as the following may occur:

- dizziness
- headache
- nausea
- vomiting
- flatulence

If these persist, speak to your doctor.

2. Kidney health

Truvada contains a formulation of tenofovir called tenofovir DF, and this drug belongs to a group of drugs called nucleotide analogues. This group of drugs is broken down by the kidneys and is associated with kidney dysfunction. There have been reports of cases of kidney dysfunction in some people who used tenofovir. People who use this drug may wish to have regular blood and urine tests done so that their doctors can assess the health of their kidneys. These tests can include the following:

- creatinine
- e-GFR (estimated-glomerular filtration rate)
- calcium
- phosphorus or phosphate
- bicarbonate

In addition to tenofovir, there are other medications which are processed by the kidneys and have the potential to cause or amplify kidney dysfunction. Many of these medications are antibiotics and are grouped as follows:

- beta-lactams – penicillin, amoxicillin
- quinolones – ciprofloxacin and related compounds
- aminoglycosides – amikacin, gentamicin
- macrolides – erythromycin
- tetracyclines – minocycline
- anti-tuberculosis agents – rifampin, ethambutol
- other antibiotics – co-trimoxazole (Septra/Bactrim), vancomycin (Vanocin), linezolid

Bear in mind that there are other medications with the potential to cause kidney dysfunction. The following is a list of medications with this potential, but this list is not exhaustive:

- antiviral agents – acyclovir (Zovirax), valacyclovir (Valtrex), cidofovir (Vistide), foscarnet (Foscavir), indinavir (Crixivan)
- antifungal agents – amphotericin B (Fungizone), intravenous pentamidine
- anti-seizure drugs – phenytoin, carbamazepine, valproic acid, phenobarbital

- medicines to treat pain and inflammation – acetaminophen (Tylenol), ibuprofen (Advil, Motrin), indomethacin (Indocid), naproxen (Naprosyn), celecoxib (Celebrex), meloxicam (Mobic)
- proton pump inhibitors – omeprazole (Losec), esomeprazole (Nexium), pantoprazole (Pantoloc), rabeprazole (Pariet)
- street drugs – use of cocaine has also been linked to kidney injury

3. Bone health

Truvada contains tenofovir. In experiments on monkeys using tenofovir at doses 10 to 30 times greater than would be used in people, the animals' bones became thinner over a period of one year.

Before you start taking tenofovir, tell your doctor if you have bone problems or thinner-than-normal bones (osteopenia or osteoporosis).

In clinical trials of regimens containing tenofovir in people with HIV, thinner bones in the spine and elsewhere have occurred. Thinner bones are generally weaker and are at increased risk for breaking (fractures) should accidents or trauma occur.

Researchers are not certain why bone thinning may occur in some people exposed to tenofovir. One theory is that bones became thinner because tenofovir may have injured the kidneys. The kidneys filter blood, putting waste materials into the urine and returning nutrients back to the blood. In the cases of tenofovir-associated bone loss, damaged kidneys may not be able to restore bone-building nutrients back to the blood.

An analysis with data from several thousand HIV-positive people has found that when boosting agents, such as cobicistat or ritonavir were used in regimens containing tenofovir DF, there was a statistically increased risk for thinning bones, bone fractures and kidney injury. Ritonavir is sold under the brand name Norvir and in generic formulations. It is also found in a medicine called Kaletra (lopinavir + ritonavir). Cobicistat is sold as Tyboost and is found with tenofovir DF in the combination tablet Stribild.

Bear in mind that some people can develop thinner-than-normal bones without ever using tenofovir. It may be useful for you to discuss with your doctor the possibility of having bone density assessments done before you begin taking tenofovir or any other anti-HIV therapy. If your bones are thin, your doctor may suggest that you increase your intake of calcium and vitamin D_3. Regular monitoring of bone density may also be useful.

Risk factors for thinning bones include the following:

- smoking tobacco
- excessive intake of alcohol
- not enough calcium in the diet
- not enough vitamin D in the blood
- being thinner than normal (having a less than ideal body mass index)
- severe kidney or liver disease
- in men low testosterone levels
- women who are undergoing menopause or who are post-menopausal, as the amount of estrogen in the body decreases during these transitions

In addition, there are many medicines that can in some cases, reduce bone density including the following groups of drugs:

- antiseizure medicines
- antidepressants
- proton pump inhibitors (used to reduce stomach acid)
- some transplant medicines including cyclosporine (Neoral) and tacrolimus (Prograf)
- steroids (corticosteroids, glucocorticoids) such as prednisone when used orally for more than three consecutive months

(For more information about vitamin D and bones, see CATIE's *A Practical Guide to Nutrition for People Living with HIV* and *A Practical Guide to a Healthy Body for People Living with HIV*.)

4. Pregnancy

Limited studies in pregnant women and animals suggest that Truvada does not appear to increase the risk of birth defects in the fetus.

The manufacturer recommends that Truvada "should be used in pregnant women only if the potential benefits outweigh the potential risks to the fetus."

5. Skin discolouration

In very rare cases, darker skin has developed on the palms and the soles of the feet in people exposed to FTC. The reason for this is not clear. However, this side effect does not appear to be harmful.

Drug interactions

Always consult your doctor and pharmacist about taking any other prescription or non-prescription medication, including herbs, supplements, and street drugs.

Some drugs can interact with tenofovir or FTC, increasing or decreasing their levels in your body. Increased drug levels can cause you to experience side effects or make pre-existing side effects worse. On the other hand, if drug levels become too low, HIV can develop resistance and your future treatment options may be reduced.

It may also be necessary to avoid drugs that do not affect levels of the medications contained in Truvada, but cause similar side effects.

If you must take a drug that has the potential to interact with your existing medications, your doctor can do the following:

- adjust your dose of either anti-HIV drugs or other medications
- prescribe different anti-HIV drugs for you

Drug interactions with Truvada

The following lists contain drugs that interact or have the potential to interact with the medications in Truvada (tenofovir and FTC). These lists are not exhaustive.

The manufacturer recommends that caution be used with the following drugs as there is the potential for serious drug interactions:

- atazanavir (Reyataz) + ritonavir (in Norvir and generic formulations)
- lopinavir/ritonavir (in Kaletra and generic formulations)
- darunavir (Prezista and in Prezcobix)

Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes are called mutations and can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you. Combining Truvada with at least one other anti-HIV drug, such as a non-nuke, integrase or protease inhibitor, can significantly delay or prevent the development of drug resistance.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed, or not taken as prescribed, levels of tenofovir DF and FTC in the blood may fall too low. If this happens, a drug resistant strain of HIV can develop. If you miss doses when taking Truvada as PrEP, you may increase the risk of becoming infected with a strain of HIV that may be resistant to the drugs in Truvada. If you find you are having problems taking your medications as directed, speak to your doctor and nurse about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future therapies might be, at some point your doctor can have a small sample of your blood analysed using resistance testing.

Should HIV in your body become resistant to the medicines in Truvada, your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

Dosage and formulations

Truvada is available as tablets, each containing 200 mg FTC and 300 mg tenofovir. The standard adult dose of Truvada is one tablet daily, with or without food, in combination with other anti-HIV medications. When used as part of a package of HIV prevention tools, the standard dose of Truvada is one tablet once daily, taken every day. Truvada is also available in generic formulations. Like all medicines, Truvada should always be taken as prescribed and directed.

Availability

Truvada is licensed in Canada for the treatment of HIV infection in adults, in combination with other anti-HIV drugs. In February 2016, Health Canada also licensed Truvada for HIV prevention when used as part of a package of HIV prevention tools. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

References

Gilead Sciences. Truvada (emtricitabine/tenofovir disoproxil fumarate tablets). *Product monograph*. 5 July, 2018.

Beck LH, Salant DJ. Chapter 310.Tubulointerstitial diseases of the kidney. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson J, Loscalzo J. eds. *Harrison's Principles of Internal Medicine*, 20e. New York, NY: McGraw-Hill; 2018.

Hill A, Hughes SL, Gotham D, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? *Journal of Virus Eradication*. 2018 Apr 1;4(2):72-79.

Fux CA, Christen A, Zgraggen S, et al. Effect of tenofovir on renal glomerular and tubular function. *AIDS* 2007; 21(11):1483-1485.

Author(s): **SR Hosein**

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 consult as broad a range of sources as possible. Users relying on this information do so entirely at their own risk. Neither CATIE, nor any of its partners, funders, 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. The views expressed herein or in any article or publication accessed or published or provided by CATIE do not necessarily reflect the policies or opinions of CATIE nor the views of its partners and funders.

Permission to reproduce

Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

CATIE fact sheets are available for free at **www.catie.ca**

CATIE
Canada's source for HIV and hepatitis C information

CONTACT US

by telephone
1-800-263-1638
416-203-7122

by fax
416-203-8284

by e-mail
info@catie.ca

by mail
555 Richmond Street West
Suite 505, Box 1104
Toronto ON M5V 3B1

Isentress (raltegravir twice daily)

FACT SHEET

Published
2019

Summary

Isentress (raltegravir twice daily) contains the anti-HIV drug raltegravir. Isentress belongs to the class of drugs called integrase inhibitors. Isentress is taken twice daily with or without food. Overall, Isentress was well-tolerated in clinical trials. General side effects were uncommon and included headache and diarrhea; these were usually mild and temporary.

What is Isentress?

Isentress contains the anti-HIV drug raltegravir. Isentress belongs to the class of drugs called integrase inhibitors.

How does Isentress work?

Isentress works by interfering with an enzyme needed by HIV called integrase. Using Isentress greatly reduces HIV's ability to infect cells and make copies of itself.

How do people with HIV use Isentress?

Isentress is meant to be used as part of combination therapy for the treatment of HIV. Combinations of anti-HIV drugs are called ART (antiretroviral therapy).

For more information about HIV treatment, see CATIE's *Your Guide to HIV Treatment*.

For many people with HIV, the use of ART has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to greatly reduce the risk of developing a life-threatening infection or an AIDS-related cancer. Neither Isentress nor any other treatment regimen (ART) is a cure for HIV. It is therefore important that you see your doctor for checkups and lab tests on a regular basis.

Evidence shows that HIV-positive people who are on ART, engaged in care, and have an ongoing undetectable viral load are substantially less likely

CONTACT US

by telephone
1-800-263-1638
416-203-7122

by fax
416-203-8284

by e-mail
info@catie.ca

by mail
555 Richmond Street West
Suite 505, Box 1104
Toronto ON M5V 3B1

CATIE
Canada's source for HIV and hepatitis C information

to transmit HIV to others, be it through sex, when sharing equipment to use drugs or during pregnancy and birth. In fact, the evidence for sexual transmission shows that people on ART who maintain an undetectable viral load do not pass HIV to their sexual partners. For further information see the CATIE fact sheet *HIV treatment and an undetectable viral load to prevent HIV transmission*. However, it is still a good idea to use condoms because they can reduce your risk for getting and passing on other sexually transmitted infections.

Warnings

Although Isentress is generally well-tolerated, side effects can occur.

1. Skin—rash and hypersensitivity

In clinical trials, the most common side effect affecting the skin was rash; this is usually mild or moderate in severity and temporary.

Symptoms of hypersensitivity reactions can include severe rash or rash with a fever, together with lack of energy and painful muscles or joints. In severe cases additional symptoms can include peeling of the skin, blisters on the lips, swollen eyes and face, stomach cramps, and difficulty breathing. The manufacturer advises that Isentress (or any other drugs suspected of causing this reaction) should be discontinued immediately if these symptoms occur, otherwise the hypersensitivity reaction can become life threatening. If symptoms suggestive of hypersensitivity occur, see your doctor immediately or go to the emergency room of your nearest hospital or medical centre.

2. Muscles—soreness and/or weakness

Isolated cases of muscle-related weakness and aches have been reported in association with the use of Isentress. In some cases, affected people also had increased levels of the enzyme creatine kinase in the blood.

Special populations

Pregnant women

Isentress was the first integrase inhibitor approved in Canada in 2007. Data from more than 500 HIV-positive pregnant women who took Isentress twice daily as part of ART found that there was no overall increase in birth defects compared to births in HIV-negative women. This finding is encouraging. However, if you are pregnant or want to have a baby, talk to your doctor.

Older people

Clinical trials of Isentress have not included large numbers of people who are 65 years or older so its effectiveness and safety in this population is not known.

General side effects

In clinical trials, Isentress was well tolerated, generally safe and effective. However, as with any treatment, there were side effects but these were usually of mild to moderate intensity and temporary, such as the following:

- nausea
- diarrhea
- headache
- dizziness

Note that the HIV-positive people who are typically enrolled in pivotal clinical trials of HIV treatments, including Isentress, are generally young and healthy. Once a drug is approved and more widely available, it gets used by populations who are not usually in pivotal clinical trials. These people may be older and may have other health issues—such as cardiovascular disease, liver injury, kidney injury, type 2 diabetes, anxiety, depression, and substance use—that require medications or that cause symptoms. As a result, their experience of side effects may be different from those reported in pivotal clinical trials.

Uncommon side effects

These side effects occurred in less than 2% of adults in clinical trials:

Anxiety and depression

Although not common in clinical trials, a small proportion of people (less than 2%) who took Isentress-based combination therapy developed one or more of the following: depression, negative thoughts, anxiety and thoughts of suicide that in some cases led to attempted suicide.

Anxiety and depression are relatively common in HIV-positive people (regardless of whether they are on treatment or the type of treatment that they take). If you are taking Isentress and think that you may have developed anxiety or depression, speak to your doctor right away. Your doctor can help determine if you have anxiety or depression and if there is any relationship between them and the medicines that you are taking.

There have been reports of rare cases where people developed anxiety and/or depression after initiating treatment with Isentress-based regimens. Symptoms of anxiety and depression can include the following:

- becoming easily upset or angry
- feeling fearful
- excessive worry
- difficulty falling asleep or staying asleep, or waking up prematurely
- unexpected feelings of sadness
- recurrent nightmares
- prolonged feelings of sadness, anger or depression
- feeling hopeless
- loss of pleasure in everyday activities
- unexpectedly feeling tired or experiencing a lack of energy
- strange thoughts

If you experience any of the above, contact your doctor or nurse right away.

If you have thoughts of harming yourself or others, dial 911 right away.

Drug interactions

Some drugs (including prescribed and over-the-counter), herbs and supplements can interfere with the absorption and/or effectiveness of Isentress. Such interference is called a drug interaction. Some drugs can reduce the levels of Isentress in your blood. This can make Isentress less effective and lead to treatment failure, possibly reducing your future treatment options. Other drugs can raise the levels of Isentress in your blood, resulting in enhanced side effects or new side effects. Therefore it is important to disclose to your doctor and pharmacist all the supplements, drugs, and herbs you are taking.

In general, Isentress does not have many drug interactions.

This factsheet is not comprehensive and only lists some of the potential and actual drug interactions with Isentress. Speak to your pharmacist to find out more about drug interactions with Isentress.

Acid-reducing agents, laxatives, metal supplements and buffered medicines

Examples of acid-reducing agents (antacids) include the following:

- Alka-Seltzer
- Gaviscon (tablets and syrup)
- Maalox (liquid and tablets)
- Milk of Magnesia
- Pepto-Bismol
- Rolaids
- Tums

Some antacids contain calcium while others contain magnesium or aluminum; some contain combinations of these metals. Merck, the drug manufacturer, warns that antacids containing aluminum or magnesium should *not* be taken with Isentress while antacids that contain calcium can be taken with Isentress. If you need to take antacids,

speak to your pharmacist about ones that are safe for you to use. Remind your pharmacist that you are taking Isentress.

Resistance and cross-resistance

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes, called mutations, can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed or not taken as prescribed, the level of Isentress in the blood may fall too low. If this happens, the HIV in your body can become resistant to Isentress and possibly other drugs you are taking. If you find you are having problems taking your medications as directed, speak to your doctor, nurse or pharmacist about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future options might be, at some point your doctor can have a small sample of your blood analyzed to test for resistance.

Dosage

Isentress is supplied as pink tablets. Each tablet contains 400mg raltegravir. The dose recommended by Merck for adults is 400 mg taken twice daily, together with other anti-HIV drugs. Isentress can be taken with or without food.

If you forget to take a dose, Merck recommends that "you take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and go back to your regular schedule."

Availability

Isentress is licensed in Canada. Your doctor or pharmacist can tell you more about the availability and coverage of Isentress in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

References

Merck Canada. Isentress (raltegravir tablets). *Product Monograph*. 19 September, 2018.

Lee FJ, Amin J, Bloch M, et al. Skeletal muscle toxicity associated with raltegravir-based combination antiretroviral therapy in HIV-infected adults. *Journal of Acquired Immune Deficiency Syndromes*. 2013 Apr 15;62(5):525-33.

Author(s): **Hosein SR**

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 consult as broad a range of sources as possible. Users relying on this information do so entirely at their own risk. Neither CATIE, nor any of its partners, funders, 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. The views expressed herein or in any article or publication accessed or published or provided by CATIE do not necessarily reflect the policies or opinions of CATIE nor the views of its partners and funders.

Permission to reproduce

Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

CATIE fact sheets are available for free at **www.catie.ca**

CATIE
Canada's source for HIV and hepatitis C information

CONTACT US

by telephone
1-800-263-1638
416-203-7122

by fax
416-203-8284

by e-mail
info@catie.ca

by mail
555 Richmond Street West
Suite 505, Box 1104
Toronto ON M5V 3B1