



## ATRIPLA

### Summary

Atripla is the name of a fixed-dose co-formulation of three anti-HIV drugs: tenofovir, FTC and efavirenz all in one pill. Atripla is usually used by itself as combination therapy for people with HIV/AIDS. Common side effects of Atripla can include dizziness, difficulty falling asleep, trouble concentrating, rash, nausea and diarrhea. Atripla is taken once-daily on an empty stomach.

### What is Atripla?

**Atripla** is the name of a fixed-dose co-formulation of three anti-HIV drugs: tenofovir, FTC and efavirenz all in one pill. Because Atripla contains these three medications it can be used as a once-daily treatment for HIV infection.

All three medicines inside Atripla interfere with an enzyme called reverse transcriptase, which is used by HIV-infected cells to make new viruses. Since Atripla inhibits, or reduces the activity of this enzyme, this drug causes HIV-infected cells to slow down or stop producing new viruses.

### How does Atripla work?

To explain how Atripla works, we need to first tell you some information about HIV. When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. In order to make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced or blocked, production of HIV slows or stops.

The three medications inside Atripla are as follows:

- Efavirenz (**Sustiva**) – this belongs to a group or class of drugs called non-nukes or NNRTIs
- tenofovir (**Viread**) – this belongs to a group of drugs called nucleotide analogues
- FTC (emtricitabine, **Emtriva**) – this belongs to a group of drugs called nucleoside analogues or nukes

### How do people with HIV/AIDS use Atripla?

Atripla, because it contains several anti-HIV drugs, is called highly active antiretroviral therapy, or HAART. For more information on HAART, see CATIE's *Practical Guide to HAART for People Living with HIV/AIDS* at [www.catie.ca/PG\\_HAART\\_e.nsf](http://www.catie.ca/PG_HAART_e.nsf).

For many people with HIV/AIDS (PHAs), the use of HAART has increased their CD4+ cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to reduce the risk of developing a life-threatening infection. Neither Atripla nor any other anti-HIV medication is a cure for HIV/AIDS. It is therefore important that you do the following:

- see your doctor regularly so that he/she monitors your health



- continue to practise safer sex and take other precautions so as not to pass HIV on to other people and protect yourself from different strains of HIV and other germs

## Warnings

### 1. Mental health

Atripla contains efavirenz. Some people who use efavirenz may experience problems with unusual thoughts and feelings, such as:

- you become easily upset or angry
- you have unexpected feelings of sadness
- you feel hopeless
- you have strange thoughts
- you have thoughts about harming yourself or others
- you have thoughts about suicide

Once you have started taking efavirenz, if you notice any of these problems, talk to your doctor right away.

### 2. Pregnancy

Pregnant women should not take Atripla because it contains efavirenz. If you are a woman who is pregnant or wants to have a baby, and you are taking Atripla, let your doctor know right away. Efavirenz has caused birth defects in infants born to pregnant monkeys and babies born to women who used efavirenz while pregnant. Efavirenz may weaken the effectiveness of hormonal contraceptives—the “pill”, implants or injections. The manufacturer suggests that women use barrier methods of preventing pregnancy, such as condoms, if they are taking efavirenz.

### 3. Hepatitis B

The safety of Atripla in people co-infected with both HIV and hepatitis B virus (HBV) is not known. Atripla contains tenofovir and this latter drug has anti-HBV activity. Co-infected people who take Atripla and then later stop may experience worsening HBV co-infection. If you have this co-infection, talk to your doctor

before you start Atripla. If you later need to change your therapy, remind your doctor that you have HBV.

### 4. Marijuana testing

In some cases, people taking Atripla, because it contains efavirenz, may falsely test positive for marijuana in drug screening assays or tests. These tests detect chemicals found in marijuana which are released into urine. According the manufacturer of efavirenz, a confirmatory test (using gas chromatography or mass spectrometry) will clear up the matter by revealing the presence of efavirenz and not chemicals found in marijuana. This information may be useful to people taking Atripla who have to undergo drug testing for various reasons. Tests used in Canada to detect marijuana include the following:

- Microgenics' Cedia Dau multilevel THC assay
- Diagnostic Reagents' Cannabinoid ELISA
- Abbott's AxSYM (also a Cannabinoid ELISA)

## Side effects

### 1. Central nervous system

Atripla contains efavirenz. The most common side effects from efavirenz affect the central nervous system (CNS), and include the following:

- dizziness
- difficulty falling asleep
- difficulty concentrating
- feeling drowsy during the daytime

Less common CNS side effects are:

- vivid dreams (these may be pleasant or unpleasant)
- hallucinations

CNS side effects occur in at least half of PHAs who use efavirenz and usually appear on the first or second day of therapy. Common CNS side effects—dizziness, difficulty falling asleep, drowsiness, decreased concentration—should



begin to fade within the first month of taking efavirenz. Some doctors suggest taking efavirenz at bedtime to reduce its impact on your ability to fall asleep. If you are having difficulty coping with these or any other side effects, let your doctor know. Use of alcohol and street drugs may make efavirenz's CNS side effects worse.

## 2. Rash

Rash can develop in some efavirenz users, including those who taking Atripla. Usually the rash occurs during the second week of therapy. Let your doctor know right away if this happens. Usually, rash associated with efavirenz is not severe and goes away after about two weeks without special treatment. Sometimes your doctor may prescribe medication, such as antihistamines, to help ease the irritation of the rash.

In rare cases the rash may become severe and other symptoms may occur such as blisters on the skin, itchy eyes, swelling, and muscle or joint pain. If this happens call your doctor immediately.

## 3. 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 people who have used the medicines contained in Atripla or related anti-HIV drugs. Women who are overweight are at increased risk for lactic acidosis. Sometimes the liver of a person with lactic acidosis becomes 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.

## 4. Liver enzymes

Increased levels of liver enzymes have been reported in some users of efavirenz, which is found in Atripla. In some cases, this may be an indicator of liver damage.

## 5. Breast enlargement in men

Temporary breast enlargement has been reported in a small proportion of men using HAART regimens, including some that took efavirenz, which is found in Atripla. Generally, this problem cleared when the men stopped taking efavirenz.

Breast enlargement has also been reported in other men who used HAART regimens without efavirenz. This problem can occur in men, particularly under the following conditions:

- having less-than-normal levels of testosterone
- use of drugs that impair the production of, or activity of testosterone – ketoconazole (**Nizoral**), metronidazole (**Flagyl**), cimetidine (**Tagamet**), flutamide (**Euflex**)
- use of growth hormone
- having higher-than-normal levels of thyroid hormones (hyperthyroidism)
- use of street drugs – marijuana, heroin
- the presence of liver disease

If breast enlargement does occur while you are taking HAART, speak to your doctor about this as there may be several options for managing this condition.

## 6. Bone health

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



In clinical trials of regimens containing tenofovir, thinner bones in the spine and elsewhere in the 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 appears to have caused the kidneys to malfunction. The kidneys filter blood, putting waste materials into the urine and returning nutrients back to blood. In the cases of tenofovir-associated bone loss, damaged kidneys may not be able to restore bone-building nutrients back to the blood.

Bear in mind that some people with HIV/AIDS 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 Atripla 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<sub>3</sub>. Regular monitoring of bone density may also be useful.

For further information about vitamin D and bones, see CATIE's *Practical Guide to Nutrition for People Living with HIV* at [www.catie.ca/ng\\_e.nsf](http://www.catie.ca/ng_e.nsf).

## 7. Kidney health

Atripla contains tenofovir, which is broken down by the kidneys. There have been reports of cases of kidney dysfunction in some people who used tenofovir. Atripla users 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
- bicarbonate

In addition to tenofovir, there are other medications which are processed by the kidneys and have the potential to damage these organs. Many of these medications are antibiotics and are grouped as follows:

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

Bear in mind that there are other medications with the potential to damage the kidneys. The following is a list of medications with this potential, 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
- NSAIDs (non-steroidal anti-inflammatory drugs) – acetaminophen (**Tylenol**), ibuprofen (**Advil, Motrin**), indomethacin (**Indocid**), naproxen (**Naprosyn**)

## 8. Lipodystrophy syndrome

In 2007 two clinical trials in the U.S. suggested that the use of efavirenz, which is found in Atripla, is associated with a significantly increased risk for changes in body shape. Efavirenz use is also linked to an increased level of cholesterol in the blood. These changes are part of a larger set of changes known as the lipodystrophy syndrome.

The HIV lipodystrophy syndrome is the name given to a range of symptoms that can develop over time when people use HAART regimens.



Some features of the lipodystrophy syndrome include:

- loss of fat just under the skin (subcutaneous fat) in the face, arms, and legs
- bulging veins in the arms and/or legs due to the loss of fat under the skin
- increased waist and belly size
- fat pads at the back of the neck (“buffalo hump”) or at the base of the neck (“horse collar”)
- small lumps of fat in the abdomen
- increased breast size (in women)

Together with these physical changes, lab tests of your blood may detect the following:

- increased levels of fatty substances called triglycerides
- increased levels of LDL-cholesterol (low-density lipoprotein), or “bad” cholesterol
- increased levels of sugar (glucose)
- increased levels of the hormone insulin
- decreased sensitivity to insulin (insulin resistance)
- decreased levels of HDL-cholesterol (high-density lipoprotein), or “good” cholesterol

The precise causes of the HIV lipodystrophy syndrome are not clear and are difficult to understand because in some PHAs there may be one or more aspects of the syndrome taking place. For instance, some people may experience fat wasting, others fat gain, and others may experience both fat gain and wasting. What is becoming increasingly clear is that unfavourable changes in the lab readings of glucose, cholesterol, and triglycerides over a period of several years increase the risk of diabetes and cardiovascular disease. So far, however, the many benefits of HAART are much greater than the increased risk of cardiovascular disease or other side effects.

Maintaining a normal weight, eating a healthy diet, exercising regularly, and quitting smoking

are all important in helping you to reduce your risk of diabetes, heart disease and other complications. Regular visits to your doctor for checkups and blood tests are a vital part of staying healthy. If necessary, your doctor can prescribe lipid-lowering therapy.

Researchers are studying the lipodystrophy syndrome to try to discover ways of helping PHAs avoid or reduce this problem. To find out more about options for managing aspects of the lipodystrophy syndrome, see CATIE’s *Practical Guide to HIV Drug Side Effects* at [www.catie.ca/sideeffects\\_e.nsf](http://www.catie.ca/sideeffects_e.nsf).

## 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 the drugs in Atripla, 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 Atripla, 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 your anti-HIV drugs or other medications
- prescribe different anti-HIV drugs for you

## Drug interactions with Atripla

The following lists contain drugs that interact or have the potential to interact with efavirenz (in Atripla). These lists are not exhaustive.



The manufacturer recommends that the following drugs should not be taken by people using efavirenz (found in Atripla) because this could lead to serious (or life-threatening) interactions.

- antihistamines – astemizole (**Hismanal**)
- anti-migraine drugs (ergot derivatives) – dihydroergotamine (**Migranal**), ergotamine (**Ergomar**), **Ergonovine**
- anti-anxiety agents – midazolam (**Versed**), triazolam (**Halcion**)
- gastrointestinal motility drugs – cisapride (**Prepulsid**)
- antifungal drugs – voriconazole (**Vfend**)
- antipsychotic agents – pimozide (**Orap**)

### Related drugs

The following anti-HIV medications should not be taken by Atripla users because they are already inside Atripla:

- efavirenz (**Sustiva**)
- FTC (emtricitabine, **Emtriva**)
- tenofovir (**Viread**, **Truvada**)

Because FTC is closely related to another drug called **3TC** (lamivudine), Atripla users should not also take the following drugs which also contain 3TC:

- **Combivir** (3TC and AZT)
- **Kivexa** (3TC and abacavir)
- **Trizivir** (AZT and 3TC and abacavir)
- **3TC** (lamivudine)
- **Heptovir** (3TC)

The following drugs can *increase* levels of efavirenz in your body:

- anti-HIV drugs – ritonavir (**Norvir**)

The following drugs can *decrease* levels of efavirenz in the blood:

- antibiotics / anti-tuberculosis drugs – rifampicin
- herbs – St. John's wort

Atripla contains efavirenz, which can *decrease* levels of the following drugs:

- antibiotics – clarithromycin (**Biaxin**), rifabutin (**Mycobutin**)
- anti-tuberculosis drugs – rifampin
- antidepressants – sertraline (**Zoloft**)
- antifungal drugs – itraconazole (**Sporanox**), ketoconazole (**Nizoral**)
- anti-HIV drugs – amprenavir (**Agenerase**), fosamprenavir (**Telzir**), indinavir (**Crixivan**), lopinavir (in **Kaletra**), ritonavir (**Norvir**), and saquinavir (**Invirase**), darunavir (**Prezista**), nelfinavir (**Viracept**)
- anti-seizure drugs – carbamazepine (**Tegretol**), phenytoin (**Dilantin**), phenobarbital
- blood thinners – warfarin (**Coumadin**)
- cholesterol-lowering drugs – atorvastatin (**Lipitor**), pravastatin (**Pravachol**), simvastatin (**Zocor**)
- drugs for high blood pressure – calcium channel blockers such as diltiazem (**Dilitaz**, **Dilitazem**), felopidine (**Renedil**), nifedipine (**Adalat**) and verapamil (**Verap**, **Tarka**)
- narcotics – methadone (your dose of methadone may need to be increased if you use efavirenz)

Atripla contains tenofovir, which can interact with the following medications by raising or lowering their levels. Or these drugs may change tenofovir levels:

- ddl (**Videx**, **Videx EC**)
- lopinavir (in **Kaletra**)
- atazanavir (**Reyataz**)

## Resistance, cross-resistance and treatment interruption

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 three drugs together, as in Atripla, delays 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 the drugs in Atripla in the blood may fall too low. If this happens, resistant virus can develop. 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.

If you stop taking Atripla, low levels of efavirenz can remain in your body up to two or three weeks. In the absence of combination therapy, these low levels of efavirenz are not high enough to suppress HIV and can lead to the development of HIV that is resistant to efavirenz. Therefore, if you are taking efavirenz and need to interrupt your therapy, speak to your specialist about ways of minimizing the chance that HIV in your body might become resistant to efavirenz. HIV that is resistant to efavirenz will usually also be resistant to other NNRTIs such as delavirdine and nevirapine (**Viramune**).

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 Atripla, your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

## Dosage and formulations

**Atripla** is available as pink tablets. Each tablet contains the following medications:

- efavirenz – 600 mg

- FTC – 200 mg
- tenofovir – 300 mg

The adult dose is one tablet at bedtime.

## Availability

Atripla is licensed in Canada for the treatment of HIV infection in adults. Your doctor can tell you more about the availability and coverage of Atripla in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* (on CATIE's website at [www.catie.ca/eng/Publications/drugaccess/drugaccessIndex.shtml](http://www.catie.ca/eng/Publications/drugaccess/drugaccessIndex.shtml)) also contains information about Canadian drug coverage.

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Author: SR Hosein

Design: Renata Lipovitch

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## Disclaimer

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

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## Contact CATIE

**by telephone**

1.800.263.1638

416.203.7122

**by fax**

416.203.8284

**by e-mail**

info@catie.ca

**on the Web**

http://www.catie.ca

**by mail**

505-555 Richmond Street West

Box 1104

Toronto ON M5V 3B1 Canada

