Atripla

FACT SHEET

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Summary

Atripla is the name of a fixed-dose pill containing three anti-HIV drugs: tenofovir DF, FTC and efavirenz. Atripla is a complete treatment for people with HIV. Common side effects 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 pill that contains the following three anti-HIV drugs:

- efavirenz (Sustiva), which belongs to a group or class of drugs called non-nucleoside reverse transcriptase inhibitors (NNRTIs or "non-nukes")
- tenofovir DF, which belongs to a group of drugs called nucleotide analogues ("nukes")
- FTC (emtricitabine), which belongs to a group of drugs called nucleoside analogues ("nukes")

Atripla can be used as a once-daily treatment for HIV infection.

How does Atripla 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. All three medicines in Atripla interfere with an enzyme called reverse transcriptase, which is used by HIV-infected cells to make more HIV. 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 do people with HIV use Atripla?

Atripla is a combination of three anti-HIV drugs. Such combinations are called antiretroviral therapy, or ART. For more information on ART, 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 reduce the risk of developing a life-threatening infection.

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Neither Atripla 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.

Warnings

1. Suicide risk

Atripla contains efavirenz. In a review of several studies comparing 3,241 efavirenz users with 2,091 non-users, researchers found that in a small proportion of people, about 2%, there was an increased risk of suicide-related behaviour among people who used efavirenz. These behaviours included the following:

- thoughts of suicide
- attempts at suicide
- completed suicide

This elevated risk of suicide-related behaviour was double that seen in people who did not use efavirenz.

Before you start therapy with Atripla let your doctor know right away if you have ever had any of the following:

- thoughts of, or attempted suicide
- a history of using street or club drugs
- anxiety or excess worry
- depression
- bipolar disorder
- difficulty falling asleep or staying asleep

Tell your doctor how much and how often you drink alcohol.

After you start therapy with Atripla: if you have thoughts of suicide or harming yourself while taking Atripla, contact your doctor immediately or call emergency services by telephoning 911.

2. Mental health

Some people who use efavirenz (one of the drugs in Atripla) may experience problems with thoughts and feelings. For example, you may:

- become easily upset or angry
- have unexpected feelings of sadness
- have prolonged feelings of sadness, anger or depression
- feel hopeless
- have loss of pleasure in everyday activities
- feel fearful
- unexpectedly feel tired or experience a lack of energy
- have difficulty falling asleep, staying asleep or waking up prematurely
- have strange thoughts
- have thoughts about harming yourself or others
- have thoughts about suicide

If you notice any of these problems before or after you have started to take Atripla, talk to your doctor right away.

3. Pregnancy and contraception

If you are a woman who is pregnant or trying to get pregnant, and you are taking Atripla, let your doctor know right away. Efavirenz has caused birth defects in infants born to pregnant monkeys and in some babies born to women who used the drug while pregnant. The manufacturer of Atripla

recommends that: "Pregnancy should be avoided in women who are taking Atripla and for 12 weeks after discontinuation."

Efavirenz may weaken the effectiveness of hormonal contraceptives—the "pill," implants or injections. The manufacturer suggests that women taking Atripla use barrier methods to prevent pregnancy, such as condoms.

4. Hepatitis and liver health

The manufacturer recommends that Atripla not be used by people with moderate or severe liver injury.

The safety of Atripla in people co-infected with HIV and hepatitis B is not known. Atripla contains tenofovir DF, which has anti-HBV activity. Co-infected people who take Atripla and then stop it may notice their hepatitis B infection worsen. 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 hepatitis B.

People who are co-infected with HIV and hepatitis-causing viruses and who take ART are at increased risk for liver toxicity. It is important to have regular blood tests so that your doctor can assess the health of your liver. If lab tests reveal that you do not have HBV, speak to your doctor about getting a vaccine to protect you from HBV.

5. Pancreatitis

Painfully swollen pancreas glands have been reported by some people taking tenofovir DF (one of the drugs in Atripla) as part of ART. Higher-than-normal levels in the blood of the enzyme amylase (made by the pancreas gland) have been detected in people taking tenofovir. This increase may suggest 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.

6. Abnormal heart rhythms

Efavirenz, in Atripla, can cause abnormal heart rhythms. Symptoms related to this can include feeling faint or fainting, or seizures. If you or a close relative (mother, father, sister, brother) have a history of heart problems including abnormal heart rhythms, let your doctor know right away.

7. Marijuana testing

Some people who take efavirenz (one of the drugs in Atripla) may falsely test positive for marijuana in drug screening tests. These tests detect chemicals found in marijuana, which are released into urine. According to the manufacturer of efavirenz, a confirmatory test 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.

8. Different strains of HIV

There are many strains or subtypes (also called clades) of HIV, such as A, B, E and others. Clade-B HIV is most commonly found in North America and Western Europe. However, due to travel and immigration, other clades of HIV can also be found in these regions. Efavirenz is effective against many different types of non-B clades of HIV. However, laboratory tests have found that efavirenz is not as effective against strains of HIV called "group O." For more information about the strain of HIV that you have, speak to your doctor.

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 include:

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

CNS side effects occur in at least half of people with HIV who use efavirenz and usually appear on the first or second day of therapy. Common CNS side effects (dizziness, difficulty falling asleep, difficulty concentrating, drowsiness) should begin to fade within the first month of taking efavirenz. Some doctors suggest taking efavirenz at bedtime to make its side effects more tolerable. If you are having difficulty coping with these or any other side effects, let your doctor know right away. Use of alcohol and street or club drugs may make efavirenz's CNS side effects worse.

In rare cases efavirenz may cause seizures. If you have a history of seizures let your doctor know before you start taking efavirenz.

2. Rash

Some people who take Atripla develop a rash. Usually the rash occurs during the second week of therapy. Let your doctor know right away if this happens. Rash associated with efavirenz is usually not severe and goes away after about two weeks without special treatment. 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

Some people who have used the medicines contained in Atripla or related anti-HIV drugs have experienced a condition called lactic acidosis—higher-than-normal levels of lactic acid in the blood. 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 by 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 by a small proportion of men using ART regimens, including some who took efavirenz (one of the drugs in Atripla). Generally, this problem cleared when the men stopped taking efavirenz.

Breast enlargement has also been reported in other men who used ART regimens without efavirenz.

This problem can occur in men, particularly under the following conditions:

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

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

6. Bone health

Atripla contains tenofovir DF. In experiments on monkeys using tenofovir at doses 10 to 30 times greater than the dose that would be used in people, the animals' bones became thinner over a period of one year. Also, taking efavirenz (one of the drugs in Atripla) may reduce levels of vitamin D in your body. Vitamin D is needed to absorb calcium and to help strengthen bones.

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

In clinical trials of regimens containing tenofovir, thinner bones and bone pain have been reported. 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 occurs 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 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 can develop thinner-than-normal bones without ever using tenofovir. This sometimes occurs in people who use ART. The decrease in bone density tends to stabilize within a couple of years after starting ART. 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, talk to your doctor about your intake of calcium and vitamin D_3. Regular monitoring of bone density may also be useful.

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

7. Kidney health

Atripla contains tenofovir DF, which is broken down by the kidneys. There have been reports of cases of kidney dysfunction and kidney failure in some people who used tenofovir DF. Atripla users may wish to have regular blood and urine tests done so that their doctors can assess the health of their kidneys. These can include tests to measure the following:

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

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

- 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 that can have the potential to cause kidney dysfunction, including (but not limited to) the following:

- 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)
- transplant drugs—cyclosporine (Neoral, Sandimmune)

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 ART. These 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, blood tests may detect the following:

- increased levels of fatty substances called triglycerides
- increased levels of LDL-cholesterol (lowdensity lipoprotein), or "bad" cholesterol
- decreased levels of HDL-cholesterol (highdensity lipoprotein), or "good" cholesterol
- increased levels of sugar (glucose)
- increased levels of the hormone insulin
- decreased sensitivity to insulin (insulin resistance)

The precise causes of the HIV lipodystrophy syndrome are not clear and are difficult to understand because some people with HIV may experience one or more aspects of the syndrome. For instance, some people may experience fat wasting, others fat gain, and others may experience both fat wasting and gain. What is becoming increasingly clear is that unfavourable changes in levels of glucose, cholesterol and triglycerides over a period of several years increase the risk of diabetes and cardiovascular disease.

Maintaining a normal weight, eating a healthy diet, exercising regularly and quitting smoking are all important to help 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 lipodystrophy syndrome to try to discover ways to help people with HIV avoid or reduce this problem.

To find out more about options for managing aspects of lipodystrophy syndrome, see CATIE's *A Practical Guide to HIV Drug Side Effects*.

Drug interactions

Always consult your doctor and pharmacist about taking any other prescription or nonprescription 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 the dose of either your anti-HIV drugs or other medications; or
- prescribe different anti-HIV drugs for you.

The following lists of drugs interact or have the potential to interact with efavirenz (one of the drugs 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, even life-threatening, interactions:

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

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, Ginkgo biloba

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—fosamprenavir (Telzir), indinavir (Crixivan), lopinavir (in Kaletra), ritonavir (Norvir), 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), felopdipine (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 DF, which can interact with the following medications by raising or lowering their levels. These drugs may also change tenofovir levels:

- ddI (Videx, Videx EC)
- lopinavir (in Kaletra)
- atazanavir (Reyataz)

Tell your doctor if you are taking the anti-HIV drug maraviroc (Celsentri) as this can interact with efavirenz in Atripla.

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, called mutations, can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you. Using a combination of drugs, such as Atripla, can delay the development of 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 for 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 cause HIV to become resistant to efavirenz. Therefore, if you are taking efavirenz and need to interrupt your therapy, speak to your specialist about ways to minimize 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 rilpivirine (Edurant), nevirapine (Viramune) and delavirdine (Rescriptor).

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 analyzed using resistance testing.

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

Dosage and formulations

Atripla comes in the form of pink tablets. Each tablet contains the following medications:

- efavirenz—600 mg
- FTC—200 mg
- Tenofovir DF—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* also contains information about Canadian drug coverage.

Reference

Bristol-Myers Squibb and Gilead Sciences. Atripla (efavirenz/emtricitabine/tenofovir DF) tablets. *Product monograph*. 8 June, 2017.

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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.

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