



EFAVIRENZ (Sustiva)

Summary

Efavirenz is a type of anti-HIV drug from the group commonly called non-nukes. Efavirenz is used as part of combination therapy for people with HIV/AIDS. The most common side effects of efavirenz can include dizziness, difficulty falling asleep, trouble concentrating and rash. Dosage of efavirenz depends on which other drugs are part of the anti-HIV therapy.

What is efavirenz?

Efavirenz, sold under the brand name **Sustiva** in Canada and the United States (**Stocrin** in Europe and many other parts of the world), is a type of anti-HIV drug (antiretroviral) called a non-nuke or NNRTI (non-nucleoside reverse transcriptase inhibitor). Efavirenz is used in combination with other anti-HIV drugs to treat (but not cure) HIV/AIDS.

How does efavirenz work?

To explain how efavirenz 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.

Efavirenz belongs to a group or class of drugs called non-nucleoside reverse transcriptase inhibitors. Efavirenz interferes with an enzyme called reverse transcriptase (RT), which is used by HIV-infected cells to make new viruses.

Since efavirenz inhibits, or reduces the activity of this enzyme, this drug causes HIV-infected cells to produce fewer viruses.

How do people with HIV/AIDS use efavirenz?

Efavirenz is used in combination with several other anti-HIV drugs, usually nukes (nucleoside reverse transcriptase inhibitors), and sometimes including drugs from different classes, such as protease inhibitors. Combinations such as this are 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.

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 efavirenz 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 practice safer sex and take other precautions so as not to pass HIV on to other people

Warnings

1. Mental health

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 efavirenz. If you are a woman who is pregnant or wants to have a baby, and you are taking efavirenz, let your doctor know right away. Efavirenz has caused birth defects in pregnant monkeys. 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. Marijuana testing

In some cases, people taking 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) 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 efavirenz 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

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 in the morning or in the early evening 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

As with all non-nukes, rash can develop in some efavirenz users. 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. Liver enzymes

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

4. Lipodystrophy syndrome

In 2007 two clinical trials in the U.S. suggested that the use of efavirenz 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.

5. Breast enlargement in males

Temporary breast enlargement has been reported in a small proportion of men using HAART regimens, including some that took efavirenz. 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.

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 efavirenz, increasing or decreasing its 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 efavirenz drug levels, 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 medication
- prescribe different anti-HIV drugs for you

Drug interactions for efavirenz

The following drugs interact or have the potential to interact with efavirenz. These lists are not exhaustive.

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

- antihistamines – astemizole (**Hismanal**)
- anti-migraine (ergot derivatives) – dihydro-ergotamine (**Migranal**), ergotamine (**Ergomar**), **Ergonovine**
- benzodiazepines – midazolam (**Versed**), triazolam (**Halcion**)
- gastrointestinal motility drugs – cisapride (**Prepulsid**)
- antifungal drugs – voriconazole (**Vfend**)

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

Efavirenz can *decrease* levels of the following drugs:

- antibiotics – clarithromycin (**Biaxin**)
- anti-tuberculosis drugs – rifabutin (**Mycobutin**)
- 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**; when saquinavir is used as the only protease inhibitor in a regimen)



- anti-seizure drugs – carbamazepine (**Tegretol**), phenytoin (**Dilantin**), phenobarbital
- narcotics – methadone (your dose of methadone may need to be increased if you use efavirenz)

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 efavirenz with at least two other anti-HIV drugs 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 efavirenz 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.

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

If you stop taking efavirenz, low levels of this drug 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 (**Rescriptor**) and nevirapine (**Viramune**).

High rates (50%) of virological failure have been reported in one study in PHAs using the following combination:

efavirenz + tenofovir (**Viread**) + ddl (**Videx, Videx EC**).

This likely happened because HIV quickly developed resistance to both tenofovir and ddl, even in the presence of efavirenz. These results suggest that this combination should be used with caution.

Dosage and formulations

Efavirenz is available as 600 mg tablets and 50 mg, 100 mg, and 200 mg capsules.

1. Efavirenz and two nukes (nucleoside analogues)

The recommended adult dosage is 600 mg per day, taken on an empty stomach at bedtime. Some doctors suggest that the efavirenz can be taken in divided doses – 300 mg twice daily, if side effects are too intense with a single dose. Taking efavirenz with food can raise the amount of efavirenz that gets in your blood and may cause new side effects or intensify pre-existing side effects.

2. Efavirenz with atazanavir (Reyataz)

If these drugs are used together, the manufacturer recommendation for adults is atazanavir (**Reyataz**) 300 mg and ritonavir 100 mg, both taken once daily with food. Efavirenz can be taken at a dose of 600 mg/day taken two hours after you have taken your dose of atazanavir and ritonavir.

3. Efavirenz and lopinavir/ritonavir (Kaletra)

The manufacturer recommends that efavirenz be used, in adults, at the standard dose of



600 mg/day, but that the dose of lopinavir/ritonavir (**Kaletra**) be increased to four capsules or 6.5 mL, twice daily.

Availability

Efavirenz is licensed in Canada for the treatment of HIV infection in adults, in combination with other anti-HIV drugs. Your doctor can tell you more about the availability and coverage of efavirenz 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) also contains information about Canadian drug coverage.

Credits

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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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