Etravirine (Intelence)

Summary
Etravirine is a type of anti-HIV drug called a non-nuke, or NNRTI. Common side effects of etravirine include rash, nausea and fatigue. The dose of etravirine used is usually 200 mg twice daily. This medication should always be taken right after a meal.

What is etravirine?
Etravirine, sold under the brand name Intelence, belongs to a class of anti-HIV drugs called non-nukes or NNRTIs (non-nucleoside reverse transcriptase inhibitors). Etravirine is used in combination with other anti-HIV drugs (or antiretrovirals) to treat, but not cure, HIV.

How does etravirine 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.

Etravirine interferes with an enzyme called reverse transcriptase, which is used by HIV-infected cells to make new viruses. Because etravirine inhibits or reduces the activity of this enzyme, this drug causes HIV-infected cells to produce less HIV.

Etravirine is licensed for use against HIV-1—the most common form of HIV. But laboratory experiments suggest that it should also be effective against HIV-2.

How do people with HIV use etravirine?
Etravirine is used in combination with anti-HIV drugs from other classes, usually nukes (nucleoside analogues), and protease inhibitors or integrase inhibitors. Combinations such as these are called antiretroviral therapy, or ART. For more information on anti-HIV drug combinations, see CATIE’s Your Guide to HIV Treatment.

For many people with HIV, the use of HIV drug treatment has increased their CD4 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 etravirine 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 or she can monitor your health.
- Continue to practice safer sex and take other precautions so to not pass HIV on to other people and protect yourself from different strains of HIV and other germs.

**Warnings**

Because etravirine is a relatively new medication, the full range of its side effects may not be known for many years. The following potentially serious side effects are uncommon; you may not experience any of them. However, if you do, report them to your doctor. This is not a complete list. Talk to your doctor or pharmacist about side effects to watch for.

1. **Rash—severe or life-threatening**

   Although rare, a small proportion of people using etravirine (less than 1 in 1000) have developed a severe and potentially life-threatening skin rash. A severe rash could be a sign of an allergic reaction called Stevens-Johnson syndrome. Along with a rash, the following may occur:

   - fever
   - blisters
   - sores in the mouth
   - itching or burning eyes or eyelids
   - swelling of the face, lips, tongue or other parts of the body
   - muscle or joint pain
   - tiredness
   - shortness of breath

   If you develop a rash or any of the previously listed symptoms while taking etravirine, tell your doctor right away.

2. **Liver health**

   In people with mild-to-moderate liver damage, the manufacturer notes that etravirine can be used safely. However, etravirine has not been tested in people with severe liver damage caused by hepatitis B or C. If you experience any of the following symptoms, contact your doctor right away:

   - abdominal pain
   - vomiting
   - fever
   - itching
   - yellowing of the skin or eyes
   - dark coloured urine

3. **Pancreatitis**

   Painfully swollen pancreas glands have been reported in a small proportion of people (less than 1 in 100) taking etravirine. Higher-than-normal levels in the blood of the enzyme amylase (made by the pancreas gland) have been detected in people taking etravirine. This increase may be a sign of inflammation in the pancreas gland. Symptoms of pancreatitis can include the following:

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

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

4. **Diabetes**

   Diabetes has been reported in a small proportion of etravirine users. However, because many drugs were being used by people in that report, it is not clear if etravirine caused this problem. Below is a list of...
symptoms that can be associated with diabetes—if you experience any of them, contact your doctor:

- excessive thirst
- excessive urination
- excessive eating
- unexplained weight loss
- wounds that do not heal properly
- infections

5. High blood pressure

Although rare, etravirine can cause high blood pressure. If you experience the following symptoms, contact your doctor:

- severe headache
- dizziness
- blurred vision
- nausea

6. Pregnancy

There are no well-controlled studies of etravirine in pregnant HIV-positive women. Therefore, the manufacturer recommends that etravirine “should be used during pregnancy only if the potential benefit justifies the potential risk.” If you are pregnant or plan to get pregnant, talk to your doctor so that you can find medicines that are safe for you and your baby.

Side effects

1. General

Long-term monitoring of etravirine use is underway. Etravirine is generally well-tolerated. In clinical trials, etravirine was used as part of combination therapy so it is difficult to be certain which side effects are caused by this drug. Here is a list of some symptoms reported by etravirine users in clinical trials:

- rash
- diarrhea
- nausea
- gas
- stomach pain

2. Rash—mild to moderate

In clinical trials, about 9% of people who took etravirine developed a rash. This side effect generally occurs within the second week of taking etravirine and may last for up to two weeks. It is uncommon for the rash to last past the fourth week of use. As with other non-nukes, women are more likely than men to develop a rash as a result of taking this medication. People who have had a rash in the past as a result of using other non-nukes are not at increased risk.

3. Liver health

Etravirine has not been well studied in people co-infected with HIV and hepatitis B or C. Liver enzymes (AST and ALT) were higher in some co-infected people after taking etravirine. Bilirubin is a waste product. Higher-than-normal levels of bilirubin in the blood can give the skin and eyes a yellow appearance. Yellow skin as a result of elevated bilirubin levels is called jaundice. This is not generally harmful. In clinical trials, people taking etravirine had an increased chance of developing very high levels of bilirubin in the blood.

4. Lipodystrophy syndrome

HIV lipodystrophy syndrome is the name given to a range of symptoms that can develop over time when people use anti-HIV drugs. So far, there is no link between the use of etravirine and lipodystrophy syndrome.

Some features of lipodystrophy include:

- loss of fat just 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)

In addition to 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 blood sugar (glucose)
• increased levels of the hormone 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. 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 increases in a person’s levels 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 anti-HIV drugs are much greater than the increased risk of cardiovascular disease or other side effects.

To reduce your risk of diabetes, heart disease and other complications, it is important to maintain a normal weight, eat a healthy diet, exercise regularly and, if you smoke, quit smoking. Regular visits to your doctor for checkups and blood tests are also 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 of helping people with HIV 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.

5. Cancer risk

A wide variety of studies suggest that etravirine does not increase a person’s risk of cancer. Long-term studies to check for the potential cancer-causing effects of etravirine are underway. These studies are a normal part of the drug approval process.

Drug interactions

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

Some drugs can interact with etravirine, 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.

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.

Etravirine may interact with the following drugs (this list is not exhaustive):

Non-nukes
• efavirenz (Sustiva, also in Atripla), rilpivirine (Edurant, and in Complera), nevirapine (Viramune) and delavirdine (Rescriptor)—these can all reduce levels of etravirine and should not be used by people taking etravirine.

Protease inhibitors

Etravirine can lower levels of protease inhibitors in the blood. For this reason, a person should only use
etravirine with protease inhibitors if the protease inhibitors are taken in combination with ritonavir, to maintain adequate drug levels. Some protease inhibitors should never be used with etravirine, even when they are combined with ritonavir:

- atazanavir (Reyataz) with ritonavir (Norvir)—atazanavir levels can fall by as much as 38%; therefore, it should not be used by people taking etravirine.

- fosamprenavir (Telzir) with ritonavir—fosamprenavir is converted into amprenavir in the blood. Etravirine boosts levels of amprenavir by 69%. The manufacturer of etravirine recommends that this drug not be taken by people taking fosamprenavir.

- tipranavir (Aptivus) with ritonavir—tipranavir may lower etravirine levels and so the combination should not be used.

Anti-anxiety agents
- diazepam (Valium)—the level of this drug may increase in etravirine users. So a reduction in the dose of diazepam may be necessary.

Antibiotics
- clarithromycin (Biaxin)—levels of this drug will be lowered and use of an alternative antibiotic (such as azithromycin) should be considered.

- rifampin or rifampicin (Rifadin, Rifater)—these drugs should not be used with etravirine because they significantly lower etravirine levels.

- rifabutin (Mycobutin)—if etravirine is not used with a ritonavir-boosted protease inhibitor, then rifabutin may be taken. If etravirine is also being used with a ritonavir-boosted protease inhibitor, then rifabutin should not be used as it will significantly reduce etravirine concentrations.

Antidepressants
- paroxetine (Paxil)—levels of paroxetine are not affected by etravirine. Data are not available for other antidepressants.

Antifungal agents
- fluconazole (Diflucan), itraconazole (Sporanox), posaconazole (Spirafil) and voriconazole (Vfend)—these can all increase levels of etravirine in the blood. The doses of these antifungal medications may therefore need to be adjusted and they should be used with caution.

Anti-seizure medications
- carbamazepine (Tegretol), phenytoin and penobarbital (Dilantin)—these can all significantly reduce levels of etravirine in the blood. They should not be used with etravirine.

Blood-thinning agents
- warfarin (Coumadin)—warfarin levels may increase.

Corticosteroids
- dexamethasone (Decadron), fluticasone pronionate (Advair Diskus, Flovent Diskus)—high doses of these drugs may decrease levels of etravirine in the body.

Drugs for abnormal heart rhythms (antiarrhythmics)
- amiodarone (Cordarone), bepridil (Vascor), disopyramide (Rythmodan), flecainide (Tambocor), mexiletine, lidocaine, propafenone (Rhythmol) and quinidine may interact with etravirine.

Drugs for erectile dysfunction
- sildenafil (Viagra), tadalafil (Cialis) and vardenafil (Levitra)—levels of sildenafil are reduced by etravirine so dose adjustments may be necessary. No data are available for tadalafil and vardenafil interactions; however, levels of these drugs are also expected to be reduced by etravirine.
**Herbs**

- St. John’s Wort or its extracts (hypericin, hyperforin)—this herb should **not** be used by people taking anti-HIV drugs including etravirine as it can reduce etravirine levels and increase the risk of HIV developing resistance to etravirine. St. John’s Wort also interacts with many other drugs, both prescription and over-the-counter medicines.

**Lipid-lowering medications (commonly called statins)**

- atorvastatin (Lipitor)—the dose of this drug may need to be adjusted.
- pravastatin (Pravachol)—no dose adjustment is necessary.
- lovastatin (Advicor), simvastatin (Zocor) and rosuvastatin (Crestor)—levels of these drugs in the blood may be reduced by etravirine.
- fluvastatin (Lescol)—levels of this drug may be elevated by etravirine.

**Narcotics**

- methadone—while etravirine is not expected to reduce methadone levels, it may occur. So adjustments to methadone doses may be needed if symptoms of withdrawal occur.

**Transplant drugs**

- cyclosporine (Neoral, Sandimmune), sirolimus (Rapamune), tacrolimus (Prograf)—levels of these drugs in the blood can decrease when used with etravirine. Close monitoring is needed to maintain adequate levels of these drugs.

**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 etravirine 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. If doses are delayed, missed or not taken as prescribed, levels of etravirine 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 options might be, your doctor can have a small sample of your blood analyzed using resistance testing. Should HIV in your body become resistant to etravirine, your doctor can help recommend a new drug combination for you.

**Dosage and formulations**

Etravirine (Intelence) is available in 100 mg tablets. The usual dose of etravirine for adults with HIV is 200 mg twice daily. The drug should always be taken right after a meal to ensure absorption. Taking it on an empty stomach may make it less effective.

The tablets should be swallowed whole, with water or another liquid. Do not chew the tablets.

Formulations can change, and dosages may need to be customized. All medications should always be taken exactly as prescribed.

**Availability**

Etravirine is licensed in Canada for the treatment of treatment-experienced HIV-positive adults, in combination with other anti-HIV drugs. Your doctor can tell you more about the availability and coverage of etravirine in your region. CATIE’s online module _Federal, Provincial and Territorial Drug Access Programs_ also contains information about drug coverage.
References


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.

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