



ATAZANAVIR (Reyataz)

Summary

Atazanavir is a type of anti-HIV drug called a protease inhibitor. The most common side effects associated with this drug can include nausea, headache, rash, stomach pain and yellowing of the skin and whites of the eyes. It is usually taken at a dose of 300 mg once daily along with 100 mg ritonavir (Norvir) once daily, both with food.

What is atazanavir?

Atazanavir, sold under the brand name **Reyataz**, is a type of anti-HIV (antiretroviral) drug called a protease inhibitor. Atazanavir is used in combination with other anti-HIV drugs to treat (but not cure) HIV/AIDS.

How does atazanavir work?

To explain how atazanavir works as a protease inhibitor, 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.

Atazanavir belongs to a group or class of drugs called protease inhibitors or PIs. This drug affects an enzyme called protease, which is used by HIV-infected cells to make new viruses. Since atazanavir 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 atazanavir?

Atazanavir is used in combination with several other anti-HIV drugs from different classes, such as other protease inhibitors, nukes (nucleoside analogues) and non-nukes (non-nucleoside reverse transcriptase inhibitors or NNRTIs). Combinations such as this are called highly active antiretroviral therapy, or HAART. In order for atazanavir to be effective it must be taken with at least two other anti-HIV drugs. For more information on HAART, see CATIE's *Practical Guide to HAART for People Living with HIV/AIDS* at http://www.catie.ca/PG_HAART_e.nsf.

For many people living 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 atazanavir 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

Side effects

1. General

General side effects that have been reported by some atazanavir users include the following: nausea, headache, rash, stomach pain, difficulty falling asleep, depression, and unexpected tiredness. Because atazanavir is a relatively new drug, new side effects may be reported in the future as more people use it.

2. Liver enzymes

Because atazanavir is metabolized (processed and broken down) by the liver, blood tests may show increased levels of liver enzymes, particularly in people co-infected with hepatitis B or C viruses.

3. Yellowing of the skin (jaundice) and whites of the eyes (scleral icterus)

In clinical trials, up to 8% of atazanavir users developed this problem. It occurs because levels of a waste product called bilirubin, build up in the blood of some atazanavir users. This does not damage your skin or eyes. However, if it occurs, tell your doctor right away. Should you develop jaundice or scleral icterus, your skin and eyes should return to their normal colour when you stop taking atazanavir.

4. Abnormal heart rhythms

In clinical trials, about 6% of atazanavir users developed abnormal heart rhythms. However, in most cases, this was only detectable with diagnostic testing (electrocardiogram). Should you develop feelings of dizziness or being light-headed, let your doctor know right away, as this may be a sign of abnormal heart rhythms or other atazanavir-related heart side effects.

5. Rash

About 20% of participants in controlled clinical trials of atazanavir have developed rash. However, this problem usually clears after several weeks.

6. Blood sugar

In some PHAs who use protease inhibitors, levels of sugar (glucose) in the blood become higher than normal. Prolonged bouts of higher-than-normal blood sugar levels may lead to diabetes. At least one study has found that some HIV-positive women, particularly those who are overweight, may be at increased risk for diabetes when they use protease inhibitors. Regular monitoring of your blood to assess sugar levels and other measurements will help you and your doctor be aware of changes that might suggest problems with your blood sugar. Although the risk of developing diabetes is generally low, symptoms that may be related to diabetes (increased thirst, increased urination, unexplained weight loss, fatigue and dry, itchy skin) should be discussed with your doctor.

7. Women and pregnancy

In experiments on female rats, atazanavir altered menstrual periods. This problem has not been reported in women who used the drug. In pregnant rabbits and rats, use of atazanavir has not resulted in birth defects.

Women who are pregnant and who use atazanavir may be more likely to develop higher-than-normal levels of bilirubin (hyperbilirubinemia) than women who are not using this drug. It is not clear what effect this might have on the human fetus.

There have been reports of pregnant women who used atazanavir developing serious side effects, sometimes fatal, including the lactic acidosis syndrome. Signs/symptoms of severe lactic acidosis can include the following:

- persistent nausea
- vomiting
- fatigue
- abdominal pain
- confusion
- fatty liver

Because of this and other risks, the manufacturer advises that atazanavir be used in pregnancy “only if the potential benefit justifies the potential risk to the fetus.”



8. Bleeding

Women may experience heavier menstrual periods when using protease inhibitors. Hemophiliacs who use protease inhibitors may also experience increased bleeding. If you are a hemophiliac who uses atazanavir and has this problem, let your doctor know about it.

9. Kidney stones

In rare cases, kidney stones may occur in some atazanavir users.

10. 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.

Atazanavir has been tested and used mostly in people who are new to anti-HIV drugs. Because it is a relatively new drug, the role of atazanavir, if any, in the lipodystrophy syndrome is not clear. In clinical trials, atazanavir, when used as the sole PI in a regimen, does not usually cause large increases in LDL-cholesterol. This may not always be the case when atazanavir is used with another protease inhibitor, such as ritonavir (**Norvir**).

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 atazanavir, 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.

This latter problem is a major issue with some medications—called proton-pump inhibitors—used to help reduce the symptoms of heart burn and acid reflux. Specific examples of proton pump inhibitors appear in the list under Drug interactions for atazanavir. However, sometimes other acid-reducing agents are used to help relieve heart burn. These medications, when taken at or around the same time as atazanavir can reduce the level of stomach acid and therefore significantly reduce the absorption of atazanavir. If you suffer from heartburn, speak to your doctor about ways you might be able to relieve this condition.

It may also be necessary to avoid drugs that do not affect atazanavir 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 atazanavir

Below are lists of actual and potential drug interactions. This list is not exhaustive. The manufacturer recommends that the following drugs should **not** be taken by atazanavir users:

- anticancer agents – irinotecan (**Camptosar**)
- antibiotics / anti-tuberculosis agents – rifampin (**Rifater**), rifampicin
- antihistamines – astemizole (**Hismanal**), terfenadine (**Seldane**)
- anti-psychotic drugs – pimozide (**Orap**)
- drugs for abnormal heart rhythms – amiodarone (**Codarone**), bepridil (**Vascor**), flecainide (**Tambocor**), propafenone (**Rhthmol**), quinidine

- gastrointestinal motility agents – cisapride (**Prepulsid**)
- herbs – St. John’s wort
- HIV protease inhibitor – indinavir (**Crixivan**)
- lipid-lowering agents – lovastatin (**Mevacor**), simvastatin (**Zocor**)
- migraine drugs (Ergot derivatives) – dihydroergotamine (**Migranal**), ergotamine (**Ergomar**), Ergonovine
- sedatives – midazolam (**Versed**), triazolam (**Halcion**)
- proton-pump inhibitors (used for heart burn, indigestion or ulcers) including – esomeprazole (**Nexium**), lansoprazole (**Prevacid**), omeprazole (**Prilosec**), pantoprazole (**Pantoloc**)

Atazanavir can *raise* the level of the following drugs in your body:

- antidepressants – amitriptyline (**Elavil**), desipramine (**Norpramin**), imipramine (**Tofranil**)
- antibiotics – clarithromycin (**Biaxin**), rifabutin (**Mycobutin**)
- blood thinning drugs – warfarin (**Coumadin**)
- drugs to treat erectile dysfunction – sildenafil (**Viagra**), tadalafil (**Cialis**), vardenafil (**Levitra**). Taking atazanavir with any of these drugs can lead to dangerous side effects and even death. Talk to your doctor if you have erectile dysfunction about how you might use these drugs safely
- lipid-lowering agents – atorvastatin (**Lipitor**)
- oral contraceptives – ethinyl estradiol, norethindrone
- HIV protease inhibitors – saquinavir (**Invirase**), amprenavir (**Agenerase**)
- transplant drugs – cyclosporine (**Neoral**), tacrolimus (**Prograf**), sirolimus (**Rapamune**)
- stimulants – methamphetamine (“Crystal meth”)

The following drugs can *lower* levels of atazanavir in your blood:

- antibiotics – rifabutin (**Mycobutin**)



- antacids and “buffered” medications
- HIV drugs – ddI (didanosine, **Videx**, **Videx EC**), efavirenz (**Sustiva**, **Stocrin**), tenofovir (**Viread**)

The following drugs can *raise* levels of atazanavir in your blood:

- antibiotics – clarithromycin (**Biaxin**)
- HIV drugs – ritonavir (**Norvir**), saquinavir (**Invirase**)

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 atazanavir 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 atazanavir 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. Although atazanavir can be used as the sole protease inhibitor in a regimen, leading American treatment guidelines indicate that the combination of atazanavir with a low dose of ritonavir is preferred. Taking atazanavir with low-dose ritonavir helps to raise and maintain atazanavir levels in the blood for prolonged periods. This reduces the risk of developing drug-resistant HIV and may help to preserve your future treatment options.

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

Dosage and formulations

Atazanavir is available as 150 mg, 200 mg and 300 mg capsules.

1. Atazanavir as the sole protease inhibitor in a regimen

The recommended and approved dose of atazanavir, when used as the sole protease inhibitor (PI) in a regimen, is 400 mg once daily taken with food. However, note that using atazanavir as the sole PI in a regimen is not the preferred way to use this medication.

2. Atazanavir with ritonavir (Norvir)

The recommended dosage is as follows — atazanavir 300 mg and ritonavir 100 mg, both drugs taken once daily with food. Taking atazanavir with a low dose of ritonavir is preferred by treatment guidelines, rather than using atazanavir as the only PI in a regimen.

3. Atazanavir with efavirenz

If these drugs are used together, the manufacturer recommendations are as follows — atazanavir 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.

4. Atazanavir and tenofovir

The manufacturer recommendations are as follows — atazanavir 300 mg/day, ritonavir 100 mg/day and tenofovir 300 mg/day, all drugs can be taken once-daily with food.

Experiments are underway testing combinations of atazanavir with other protease inhibitors such as saquinavir (**Invirase**) and amprenavir (**Agenerase**). In some of these



experiments atazanavir acts as a “booster” — raising levels of the other protease inhibitor in the blood for prolonged periods.

Availability

Atazanavir 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 atazanavir 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.

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2007



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Funding has been provided by the Public Health Agency of Canada.

