



Atazanavir

Atazanavir (Reyataz) is a *protease inhibitor* that received FDA approval in June 2003. Other approved drugs in this class include amprenavir, indinavir, Kaletra, nelfinavir, ritonavir and saquinavir.

Who should use it?

Atazanavir is a once-daily therapy approved for use in combination with other anti-HIV drugs in adults, regardless of prior anti-HIV therapy use. It's recommended that people receive a resistance test prior to starting the drug to increase the chance that they will benefit from it. The drug does not appear to cause large increases in cholesterol and triglyceride (lipid) levels associated with other protease inhibitors. For this reason it may be a nice option for people with cholesterol concerns and/or those with risks for heart disease. This might be particularly true among people who have never taken anti-HIV therapies or a protease inhibitor and hope to avoid cholesterol problems. It may also be useful for people who already have such problems from the use of other protease inhibitors.

When used as part of a second or *third line* therapy, in order for atazanavir to provide benefit, it may well need to be "boosted" with a small amount of ritonavir. Because ritonavir is known to have an effect on cholesterol, the advantages of atazanavir with regard to this side effect may be decreased.

What does the research show?

Three studies were particularly important in supporting the approval of atazanavir. One compared atazanavir to a commonly used NNRTI called efavirenz. Another compared atazanavir to the protease inhibitor nelfinavir. Both studies included people who had never used anti-HIV drugs. The third study compared atazanavir to the protease inhibitor Kaletra and included people who had previously used (and failed) one protease inhibitor-containing regimen. In all, CD4+ cell counts at study entries were about 300 (321 in the first, 295 in the second and 318 in the third). In the studies that looked at people who had never used anti-HIV treatment, viral loads were about 60,000 at study entry. In the study of people who had used and failed one protease inhibitor, viral load was close to 10,000 at study entry.

In the first study, 810 volunteers received Combivir (AZT+3TC, given twice daily) and either atazanavir (400mg once daily) or efavirenz (600mg once daily). Both groups had comparable decreases in viral load and rises in CD4+ cell counts. Overall, about 65% of those receiving the combinations achieved viral load suppression to below the limit of detection of the tests (400) through 48 weeks (about one year) of therapy. Those receiving atazanavir had a mean (average) CD4+ cell increase of close to 180, while those receiving efavirenz averaged increases of about 160. In general these therapies appear to be comparable in potency, though have different side effect concerns.

In the second study, 467 people were given d4T and 3TC twice daily together with either atazanavir (once daily) or nelfinavir (1,250mg twice daily). Similar percentages of people achieved viral suppression to below detectable (400) in both groups, but those on atazanavir did slightly better (67% compared to 59%) though 48 weeks. However, when using a more sensitive viral load test (limit of detection below 50) slightly more people did "better" in the nelfinavir group (38% compared to 33%). CD4+ cell count increases averaged about 234 among those taking atazanavir compared to 211 on nelfinavir. In other words, these therapies appear generally comparable in potency, though again they have differing side effect concerns.

The third study evaluated once daily atazanavir to twice daily Kaletra in combination with two NRTIs (like AZT, 3TC, d4T, etc.). Significantly more people receiving the Kaletra-based regimen achieved viral load reductions to below the limit of detection (75% compared to only 54% of those receiving atazanavir) through week 24 (6 months). When using the more sensitive viral load test, with a limit of detection of 50, these results held with 50% of Kaletra users and only 34% of atazanavir users achieving suppression to undetectable levels. Moreover, CD4+ cell count increases were more pronounced among Kaletra recipients (121 compared to 101 taking atazanavir). While Kaletra was clearly a superior option, those on Kaletra also experienced more side effects.

In a recent study presented at the International AIDS Society meeting (July 2003), atazanavir was evaluated as part of a *third line* regimen in 358 people who had failed two previous anti-HIV regimens and showed resistance to at least one drug in each class (NRTI, NNRTI and PI). Volunteers took tenofovir and a NRTI and either Kaletra, once daily combination of atazanavir (300mg)+

Atazanavir vs. efavirenz, 810 people after 48 weeks

Regimen	% viral load under 400	CD4+ cell count increase
Combivir + atazanavir	65%	+180
Combivir + efavirenz	65%	+160

Atazanavir vs. nelfinavir, 467 people after 48 weeks

Regimen	% viral load under 400	CD4+ cell count increase
Atazanavir + d4T + 3TC	67%	+234
Nelfinavir + d4T + 3TC	59%	+211





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ritonavir (100mg) or once daily combination of atazanavir (400mg) +saquinavir (1,200mg). At 24 weeks (6 months) the Kaletra and atazanvir+ritonavir groups showed comparable results, with the atazanvir+saquinavir combination falling out as inferior. Those taking the atazanavir+ritonavir combination were less likely to have increases in lipid levels, less likely to experience diarrhea, but more likely to have increases in bilirubin and associated jaundice. Because atazanavir may boost tenofovir levels, however, it's unclear if these same results would hold true if the atazanvir+ritonavir combination were used together with any NRTI two-drug backbone for a regimen. For results of an earlier study comparing atazanavir to nelfinavir, and switching from nelfinavir to atazanavir, see *PI Perspective #35*.

How to Use it?

Atazanavir comes in 100, 150 and 200mg capsules. The daily dose for adults is 400mg, once daily, to be taken with food.

Dose adjustments are required when using the drug in combination with some other anti-HIV drugs. When taken with efavirenz, it's recommended that atazanavir be used with a low dose of ritonavir. When used in this combination it's recommended that ALL of the drugs be taken only once daily at the following doses; efavirenz (600mg, taken with food), atazanavir (300mg) and ritonavir (100mg). It's further recommended that atazanavir NOT be used with efavirenz unless it is used with the low dose of ritonavir.

New information suggests that when atazanavir is used with tenofovir, it should also be used in combination with ritonavir.

When used in combination with the NRTI drug ddI and ddI EC, it is recommended that atazanavir be taken either two hours before or one hour after ddI, with food. Even with the newer extended release formulation of ddI EC, ddI EC is recommended to be taken on an empty stomach while atazanavir is recommended to be taken with food, so they should not be taken at the same time.

Other dose adjustments may be required when taking atazanavir in combination with other anti-HIV drugs as well and if people have impaired liver function.

In general, boosting with a small dose of ritonavir is recommended for most people who have developed resistance to other protease inhibitors. Atazanavir is likely to be used without ritonavir boosting only when a person is starting anti-HIV drugs for the first time.

What about side effects?

Perhaps the most attractive feature of this drug, besides the ease of use of once-daily dosing, is that, so far, studies have shown relatively few side effects. This may or may not change as doctors and patients have more and longer-term experience with the drug. One of the most common side effects of atazanavir is increases in a laboratory measure called bilirubin. This occurred in 35% and 47% of study participants in the first two studies noted above. In nearly all cases bilirubin levels returned to normal upon discontinuing the drug. In a few instances physical symptoms were asso-

ciated with this elevated lab marker, including yellowing of the skin or whites of the eyes (*jaundice*).

Atazanavir does not appear to have the pronounced impact on lipid levels (cholesterol and triglycerides) seen with most other protease inhibitor therapies. When compared to Kaletra, atazanavir appeared to cause dramatically fewer problems with lipids. Some speculate that this might lead to decreases in concerns about body composition changes (particularly fat accumulation in the truncal area, breast or base of the neck) called *lipodystrophy* associated with protease inhibitor use. Preliminary reports from a study which looked for body composition changes in people receiving either an efavirenz- or atazanavir-containing regimen with AZT+3TC show no symptoms of lipodystrophy through 48 weeks (about 1 year) of treatment. While some people receiving efavirenz had increases in lipids, no one receiving atazanavir had increases in lipids. It can't be said that atazanavir use won't be associated with lipodystrophy, certainly longer follow-up and more study is needed, but this preliminary report is encouraging.

When compared to nelfinavir or efavirenz regimens, atazanavir-containing regimens appeared to have similar or slightly fewer side effects. In general, when compared to efavirenz, slightly more people receiving atazanavir experienced nausea and yellowing of hands/eyes (*jaundice*). Some of the biggest concerns with efavirenz include sleep disturbances, mental status changes, including depression. These did not occur as often among those receiving atazanavir. With regard to nelfinavir, where the most common side effect is diarrhea, significantly fewer people experienced diarrhea with atazanavir. Also, when people who had used nelfinavir in the first part of a study were later switched to atazanavir, there were significant drops in their cholesterol levels.

Protease inhibitors have been associated with an increased risk of diabetes. In the study which compared atazanavir to efavirenz in combination with AZT+3TC, noted above, at 48 weeks no one in either group showed evidence of insulin resistance, which is a measure for risk of diabetes. Diabetes may also be less of a concern with atazanavir compared to other protease inhibitor drugs. More research is needed, however.

As with other protease inhibitors, it's possible that symptoms of hepatitis C or B may worsen upon starting atazanavir. People are encouraged to be tested for hepatitis prior to starting anti-HIV drugs and monitor liver tests carefully after starting anti-HIV therapy.

Some people taking atazanavir with other anti-HIV drugs have developed a serious and potentially life-threatening complication called *lactic acidosis*. This condition is often more associated with NRTIs, which are often used in combination with protease inhibitor drugs, including atazanavir.

What about drug resistance?

HIV resistance to atazanavir is likely to be a concern, and thus the drug should be used in combination with other anti-HIV therapies.

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Resistance to a drug occurs when the virus changes or modifies itself such that it is no longer crippled in its replication cycle by the effects of a drug. Cross-resistance is when resistance to one drug also causes resistance to other drugs. Studies suggest that cross-resistance to other protease inhibitor drugs, in particular, is likely to be a problem with atazanavir.

Once a person has developed resistance to atazanavir, they are very likely not going to benefit as well from other approved protease inhibitors. It might be possible, however, to use boosted doses of these other therapies to overcome some of this resistance. Some test tube studies suggest that even though resistance may have developed to some other protease inhibitors, atazanavir may still have some anti-HIV effect. The bottom line message, however, is that the story of atazanavir resistance is still an evolving story.

HIV and the brain

Because HIV can infect brain cells, it's important to consider a drug's ability to reach the brain when putting together an anti-HIV regimen. It's probably wise to include at least one drug that has been shown to cross the blood-brain barrier to some useful degree as part of your regimen. These include AZT (zidovudine, Retrovir), d4T (stavudine, Zerit), abacavir (Ziagen), nevirapine (Viramune), amprenavir (Agenerase), atazanavir (Reyataz) and to a lesser degree indinavir (Crixivan) and 3TC (lamivudine, Epivir). Efavirenz (Sustiva) has not been shown to cross the barrier to a significant degree, but some experts speculate that it might have some useful effect in impacting HIV in the spinal fluid.

What about drug interactions?

Atazanavir is processed through the liver and has *many* drug interactions. First and foremost, it's wise to talk to your doctor and pharmacist about ALL therapies, remedies and drugs you take (including vitamins, herbs, street drugs, etc.) and find out about potential risks for drug interactions with atazanavir. Some of these interactions may be life-threatening, others may merely require dose adjustments of the therapies.

Therapies that should *not* be taken with atazanavir because of possibly serious or life-threatening consequences include; benzodiazepines (including medazolam, triazolam—may have life-threatening consequences), ergot derivatives (dihydroergotamine, ergotamine, ergonovine, methylergonovine—may increase risks of serious life-threatening side effects of ergot derivatives), GI motility agents (cisapride—may increase risk of side effects of agents, including serious changes in heart rhythm), neuroleptics (pimozide), anti-cholesterol drugs (particularly lovastatin and simvastatin—may increase risks of side effects), pro-ton pump inhibitors (decrease atazanavir levels and increases risks of resistance), rifampin (a common anti-TB agent, may decrease blood levels of atazanavir by 90%), irinotecan (may increase side effects of irinotecan), indinavir (Crixivan, both increase bilirubin levels and may worsen this side effect of both drugs), and St John's Wort (hypericin, may decrease blood levels of atazanavir.)

Other therapies have known drug interactions and may require dose adjustments or special monitoring to increase the safety of taking them with atazanavir.

With regard to interaction with other anti-HIV therapies; ddI buffered formulation (take two hours before or one hour after ddI), ddI EC (do not take simultaneous to atazanavir, as atazanavir must be taken with food, ddI EC without), efavirenz (decrease blood levels of atazanavir, when used in combination with atazanavir, should be also used with ritonavir, see "dosing" information above), saquinavir (atazanavir increases saquinavir levels, dose adjustment recommendations not yet established), ritonavir (increases atazanavir levels, when used together, the dose of atazanavir should be reduced to 300mg once daily combined with 100mg of ritonavir once daily), tenofovir (Viread, decreases levels of atazanavir, when used in combination the ritonavir boosting scheme should be employed 300mg atazanavir with 100mg ritonavir, once daily)

With regard to other therapies with known interactions; antacids and buffered medications (reduce atazanavir blood levels, should be taken two hours before or one hour after atazanavir), anti-arrhythmics (including amiodarone, lidocaine and systemics—atazanavir may increase blood levels of these drugs, special monitoring is warranted, may increase risk of side effects, dose adjustments may be needed), warfarin (may increase warfarin levels, special monitoring is warranted to prevent bleeding), tricyclic antidepressants (may increase blood levels of tricyclics, blood level monitoring warranted), rifabutin (a common anti-MAC preventive therapy. Atazanavir may increase blood levels, dose reduction to 150mg every other day or three times a week may be needed), calcium channel blockers (diltiazem, dose reduction of diltiazem by 50% may be warranted, monitoring of blood levels of felodipine, mifedipine, nifedipine, and verapamil is warranted), sildenafil (also called Viagra. Dangerous increases in sildenafil levels, dose reduction to 25mg every 2 days may be warranted), cholesterol-inhibiting agent atorvastatin (increases atorvastatin levels, additional monitoring is warranted), H-2 receptor antagonists (may decrease blood levels of atazanavir), immunosuppressants (e.g. cyclosporine, sirolimus, tacrolimus—atazanavir increases blood levels of these drugs), clarithromycin (50% dose reduction of clarithromycin should be considered—alternative anti-MAC therapies may be preferable), oral contraceptives (atazanavir increases blood levels of oral contraceptives, lower doses of should be considered).

What is known about this drug for women, people of color, children, and the elderly?

Atazanavir has not been well studied in pregnant women and thus is generally discouraged for use in either pregnant or nursing women. It is not known if atazanavir is excreted in breast milk. Because HIV can be passed through breast milk, nursing is generally discouraged in areas where alternatives exist. Results from preliminary studies in animals do not suggest that there will be a problem with atazanavir use during pregnancy, but animal studies



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do not always predict safety in humans. There have been cases of lactic acidosis in pregnant women using anti-HIV therapies, including atazanavir. Increases in bilirubin might have more serious consequences for a developing fetus and very young children.

There is not enough information to determine if atazanavir doses need to be modified based on race or ethnicity. Atazanavir has not been well researched in children. Not enough people over the age of 65 were included in studies to provide special/unique information for the elderly to consider. However, a small study that included people over 65 years of age does not suggest dose modifications are needed based on age. Moreover, there do not appear to be differences in the way the drug is processed or cleared based on sex.

How do I get it?

Atazanavir is available by prescription at hospitals and pharmacies. Many states will likely cover atazanavir through their AIDS Drug Assistance Programs (ADAP). To find out if you're eligible for your state ADAP and if atazanavir is covered through your state's program, contact Project Inform at 1-800-822-7422. Information is also available from AIDS Treatment Data Network at 1-800-734-7104 or www.atdn.org. People who lack insurance, Medicaid, ADAP coverage or other ways to buy the drug might gain access to it through the company's Patient Assistance Program (1-800-272-4878).

Commentary

It remains a bit unclear how atazanavir fits into the arsenal of other approved protease inhibitors. The most attractive features of this drug are its ease of use (taken only once daily), and it's relatively few side effects. These features may make it of particular interest as part of *first line* therapy for treating HIV, for those who are experiencing problems with adhering to more complex medication schedules, for those who are experiencing problems with lipid elevations (increases in cholesterol and triglycerides) while using other therapies and for people who may have risks for high cholesterol and heart disease (e.g. family history, smokers, etc.).

When considering atazanavir as part of a regimen if you've never used anti-HIV therapies before, there are a few issues to consider. First, in studies atazanavir appeared to have equal potency when compared to efavirenz-containing regimens. Efavirenz is in a different class of drug (NNRTI) and it is a very popular drug for *first line* use. The advantages of starting with atazanavir as opposed to efavirenz may be that atazanavir does not have the mental status side effects associated with efavirenz (like sleep disturbances, hallucinations, etc.). Also, when someone develops resistance to efavirenz, nearly complete cross-resistance to all the other currently available NNRTIs is very likely (i.e. the other NNRTIs are likely to not work at all). While there is some evidence that resistance to atazanavir may also lead to cross-resistance to other protease inhibitors, it's less clear if this will present a major obstacle in benefiting from other protease inhibitor-containing regimens in the future. Also, because atazanavir need only be taken once daily, especially for someone starting therapy for the first time this

may be very attractive as it may decrease the interference with daily routines while a person adjusts to taking anti-HIV medications.

When it comes to atazanavir use as part of *second line* therapy, the picture becomes a little more complicated. Resistance testing will be particularly important here to help determine if a person is likely to benefit from the drug. Resistance to other protease inhibitors may decrease the effectiveness of atazanavir. In some cases, particularly where resistance may be a concern, it may be necessary to boost blood levels of atazanavir by using a small dose of another protease inhibitor called ritonavir. In these cases, some of the attractive features of atazanavir are lost to some degree. Because ritonavir is known to increase lipid levels, using the combination of the two drugs will still likely lead to risks for this side effect. With this said, however, it's likely that lipid problems will be less of a concern with this boosting regimen compared to other ritonavir-boosted regimens where the second drug may also have this side effect concern (e.g., ritonavir+indinavir, Kaletra, etc.).

Increasingly, data suggests that atazanavir use in *third line* or *salvage* situations will require ritonavir boosting. In this situation the combination of atazanavir and ritonavir may be equally potent to Kaletra and have fewer lipid-related side effects, less associated diarrhea, but higher risks for increased bilirubin and possibly jaundice.

The Bottom Line

Benefits:

- Potency is equivalent to nelfinavir or efavirenz when used as part of a three-drug combination for people have not previously used anti-HIV therapy.
- When boosted with small doses of ritonavir, may be useful as an alternative to Kaletra in people who have experienced drug failure with two other regimens.
- Does not elevate blood fats to the same degree as most other protease inhibitors.
- Once daily dosing.

Concerns:

- Must be boosted with ritonavir if used in combination with tenofovir, and even then should be used together with caution.
- Must be boosted with ritonavir if used in combination with efavirenz.
- Resistance to atazanavir may lead to resistance with other protease inhibitors.
- Has many potential drug interactions with therapies commonly used among people with HIV
- Can cause elevations in bilirubin levels.

How to Get It:

- Bristol-Myers Squibb's Patient Assistance Program, call 1-800-272-4878.
- Available through hospitals and pharmacies.
- Available through some state AIDS Drug Assistance Programs.