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# Atazanavir

## A Viewpoint by Robert L. Murphy

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Atazanavir is the latest protease inhibitor to be developed. The *in vitro* potency, pharmacokinetic properties, resistance profile, clinical efficacy and the effect on serum lipid concentrations are all favourable. Atazanavir is the first protease inhibitor that can be administered as two capsules once daily, offering a distinct advantage over other drugs within this class.

The drug is very well tolerated. Other than relatively mild gastrointestinal adverse effects, other adverse effects are rare. The only unique problem associated with atazanavir is a dose-dependant increase in indirect bilirubin. In a clinical trial up to 41% of patients administered 400 mg daily had grade 3–4 increases in bilirubin however these were clinically irrelevant, associated with jaundice only 6–12% of the time, and rarely led to discontinuation of treatment.[1] Upon discontinuation, indirect bilirubin levels returned to pretreatment values within 1–2 days. Other liver abnormalities were no more common than in comparator treatment arms.

The resistance profile to atazanavir is unique. Protease inhibitor-naive patients experiencing virological failure are likely to have the I50L signature mutation with or without the A71V substitution. The presence of I50L does not affect susceptibility to any of the other available protease inhibitors and may actually enhance it, a distinct advantage. Atazanavir is likely to be effective even in patients with virus resistant to one or two of the other protease inhibitors.

Atazanavir has excellent *in vitro* potency, with an $EC_{50}$ of 2.6–5.3 nmol/L. In treatment-naive patients, clinical efficacy was similar in atazanavir-, efavirenz- and nelfinavir-based regimens although the proportion of patients in these trials who achieved viral HIV RNA levels <50 copies/mL after 48 weeks was less than expected. It should be noted that the HIV RNA levels for some patients were measured by the more sensitive Roche Amplicor version 1.5 in these trials.

In treatment-experienced subjects, atazanavir alone was inferior to lopinavir/ritonavir, but when atazanavir/ritonavir was compared to lopinavir/ritonavir or ritonavir/saquinavir, results were similar, suggesting that treatment-experienced patients will have better outcomes with the pharmacologically enhanced or 'boosted' approach.

The most unique feature of atazanavir is the negligible effect this drug has on serum lipid levels. The modest increases associated with atazanavir most likely reflect a return to pre-HIV infection levels as suggested recently by Riddler et al.[2] Compared with efavirenz- and nelfinavir-based treatment, the difference is highly significant. The question remains whether the favourable lipid profile associated with atazanavir therapy will translate to a relative reduction in cardiovascular events.

In one study, atazanavir therapy was not associated with changes in insulin or glucose levels after 48 weeks; further evidence that atazanavir has a different metabolic profile compared to other members of its class.

In conclusion, atazanavir-based treatment offers patients a simple and well tolerated once daily alternative to non nucleoside-based approaches. For patients that fail atazanavir first line therapy, the protease inhibitor class is preserved. For treatment-experienced patients, 'boosted' atazanavir may be an option for many. Another potential use for this drug is in patients with hyperlipidaemia that would prefer switching antiretroviral therapy rather than adding lipid-lowering treatments. ▲

## References

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