Atazanavir (Reyataz™) Criteria for Use

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are dynamic and will be revised as new clinical data become available. These guidelines are not intended to interfere with clinical judgment. Rather, they are intended to assist providers in making the best clinical decisions that result in high quality, cons istent, cost-effective care. For a complete review of atazanavir, please refer to the full Drug Monograph on the PBMSHG website.

Executive Summary

VHA's HIV clinicians are able to choose the best-available ARV regimen for an individual patient based on the patient's clinical status, their past experience with ARVs, the risks of side effects, and an expectation of tolerance and a potential for benefit. Atazanavir has shown surrogate marker equivalency to efavirenz and nelfinavir in the drug naïve population and to lopinavir/ritonavir when boosted with ritonavir in the heavily pretreated population. Non-boosted atazanavir was less effective in lowering viral load when compared to lopinavir/ritonavir in the single PI experienced population. Given the price difference between atazanavir (alone or boosted) as compared to the current DHHS recommended agents, VHA HIV clinicians should be aware of the impact of prescribing atazanavir on VHA pharmaceutical budget. VHA clinicians are asked to following some simple Criteria for use when prescribing atazanavir.

- The preferred therapies for treatment naïve and treatment experienced HIV-infected patients within the VA are as per the July 2003 Department of Health and Human Services (DHHS) - Kaiser Family Foundation's Guidelines for the Use of Antiretroviral Agents in HIV Infected Adults and Adolescents Therapy.

- Use of atazanavir should be limited to treatment naïve and treatment experienced HIV-infected patients who meet the following criteria. These criteria have been more fully described in the body of this document.

  Treatment Naïve:
  - Patients with a history of cardiovascular disease or multiple risk factor for cardiovascular disease

  OR
  - Patients who would be likely to fail any regimen of HAART that requires more than once daily treatment **and** who are not candidates for therapy with other DHHS-recommended once daily regimens.

  Treatment Experienced:
  - Patients with a documented intolerance to the current *preferred* Protease Inhibitors

  OR
  - Patients clinically and/or virologically stable on an ARV regimen who are experiencing uncontrollable LDL cholesterol and/or triglycerides. Uncontrolled dyslipidemia includes patients that do not reach VHA recommended target goals with lifestyle changes and/or pharmacologic intervention.

  OR
  - Patients with documented resistance to other PI class agents where ritonavir boosted atazanavir would be expected to have activity.

I. Overview

Prescribing Antiretrovirals
VHA has adopted the Department of Health and Human Services (DHHS) - Kaiser Family Foundation's Guidelines for the Use of Antiretroviral Agents in HIV Infected Adults and Adolescents as official VA guidelines for HIV treatment (DIRECTIVE 2000-018). Recently (July 14, 2003), the DHHS guidelines have changed from recommending any of a large number of possible drug combinations in drug naïve patients to assigning preferred and alternate agents based on comparative clinical trial data, patient tolerance, pill burden, and dosing frequency. At the time these atazanavir criteria for use were developed, the preferred agents in the drug naïve population were as follows:

- ***efavirenz*** *+ (zidovudine or tenofovir or stavudine) + lamivudine as preferred initial nonnucleoside reverse transcriptase inhibitor (NNRTI)-based regimens (except for pregnant women).*
- ***lopinavir/ritonavir*** *+ (zidovudine or stavudine) + lamivudine as preferred protease inhibitor (PI)-based regimens*

The guidelines also contain a list of alternate regimens that may be selected for a given patient who may be intolerant of or have contraindications to the currently preferred agents. As these guidelines represent a living document, undergoing constant update and revision by a panel of HIV experts, VHA recommends that clinicians review the most recent version available at http://www.aidsinfo.nih.gov/guidelines.
Prescribing ARV therapy for the drug-experienced patient is more complicated than the naïve population and is beyond the scope of this document. Again, you are referred to the DHHS guidelines.

Atazanavir
Atazanavir was approved on June 20, 2003 for use in combination with other antiretrovirals (ARVs) to treat HIV-1 infection. This indication was based upon virologic (HIV viral load) and immunologic (CD4 lymphocyte count) responses during controlled clinical trials in ARV-naïve and ARV-experienced patients. Atazanavir joins 6 other antiviral agents in the protease inhibitor (PI) class on the VHA National Formulary. Atazanavir has been studied in comparative, controlled clinical trials in an ARV naïve population against efavirenz (in combination with the co-formulated product lamivudine and zidovudine, AI424-034) and nelfinavir (in combination with lamivudine and stavudine, AI424-008). In an intent-to-treat analysis (week 48), there was no statistical or clinically significance difference in virologic or immunologic surrogate markers between the atazanavir study arm and either efavirenz (AI424-034) or nelfinavir (AI424-008) among these ARV-naïve subjects. Two trials in drug experienced patients have been reported out to 24 weeks duration in patients with prior PI experience (AI424043) or with prior exposure to all three classes of ARV agents (at least 2 separate regimens, AI424045). Both clinical trials compared lopinavir/ritonavir (Kaletra®) to atazanavir alone (AI424043) or boosted with low dose ritonavir (AI424045). Given that the drug experienced population has also been previously exposed to various nucleoside analogues (nRTIs), the local treating physician was permitted to select at least one nRTI which was appropriate for a given study subject. In study AI424-043, there was a significantly greater fall in HIV RNA levels with the lopinavir/ritonavir containing regimen (-2.16 $\log_{10}$copies/ml) versus the atazanavir (-1.73 $\log_{10}$ copies/ml) containing regimen (ATV-LPVr 0.31 (97.5% CI 0.06, 0.55)). Week 24 virologic marker data recently presented for the heavily pre-treated population in study AI424045 showed equivalence between ritonavir boosted atazanavir and lopinavir/ritonavir while a third study arm investigating the combination atazanavir *plus* saquinavir showed significantly less impact on HIV viral load at week 24.

In the early Phase I/II trials for atazanavir, it was observed that lipids, including cholesterol and triglycerides, did not increase with short term exposure to the drug. This finding was contrary to what has been seen with other potent ARV regimens including all agents in the PI class, the nonnucleoside reverse transcriptase inhibitors (nnRTI), and triple nucleoside therapy with abacavir. Phase III clinical trials included secondary endpoints related to lipid abnormalities. The *fasting* lipid panel data for baseline compared to study week 24 for study AI424-034 are listed below.

	ATV+3TC/ZDV			EFV + 3TC/ZDV		
	Baseline	Week 24	Change	Baseline	Week 24	Change
n=	383	283		378	264	
Total Chol	164*	168	+2%	162	195	+21%
HDL Chol	39	43	+13%	38	46	+24%
LDL Chol**	98	98	+1%	98	114	+18%
TG	138	124	-9%	129	168	+23%

* mean data are presented with percent change from baseline ** Chol = Cholesterol, TG - triglycerides

Fasting lipid data from the drug experienced clinical trial comparing atazanavir (AI424-043) with lopinavir/ritonavir is shown below.

	ATV + optimized therapy			LPV/r + optimized therapy		
	Baseline	Week 24	Change	Baseline	Week 24	Change
n=	143	123		144	107	
Total Chol	181*	170	-2%	175	201	+17%
LDL Chol**	106	95	-6%	103	107	+5%
HDL Chol	39	41	+12%	37	45	+18%
TG	192	193	-2%	192	262	+55%

* mean data are presented with percent change from baseline ** Chol = Cholesterol, TG - triglycerides

The mean patient age in these clinical trials were 34 and 38 years, respectively. The average age for HIV positive veterans in the National Immunology Case Registry (NICR) database for patients in care during FY2002 was 50 years. How lipid profiles will be modulated by atazanavir in such an older population remains to be seen.

Tolerance and Side Effects

The more frequently reported side effects to atazanavir during clinical trials included nausea, vomiting, diarrhea, abdominal pain, jaundice/scleral icterus, depression, hyperbilirubinemia, and rash. Hyperbilirubinemia at NIAID toxicity grades 3/4 was experienced by 22-40% of the patients during clinical trials. The mechanism for this effect is the direct inhibition of bilirubin conjugation (UDP-glucuronyl transferase – (UGT)) by atazanavir.

Cost Impact

Whether used alone or in a ritonavir-boosted format, atazanavir is substantially more expensive to VHA than the DHHS preferred agents (efavirenz or lopinavir/ritonavir) – see below. Limited data are available on the potential impact (clinical and economic) of metabolic complications (specifically dyslipidemias) related to ARV use, including monitoring for disease, therapeutic intervention, and significant clinical events (e.g., acute myocardial infarction), making it currently not possible to factor in any financial impact atazanavir might have on short-term metabolic or cardiovascular outcomes. As mentioned above, the average age for VHA HIV positive patients is 50 years making extrapolation of lipid panel data collected on a population with a mean age of 34 difficult. Comparisons between atazanavir and the DHHS preferred agents may be possible once more long-term clinical outcomes data (>2 years) become available for atazanavir.

II. Patient Selection for Atazanavir Treatment

VA clinicians considering the use of atazanavir are requested to follow some general criteria for use for each patient considered as a candidate for therapy. The criteria were designed from the clinical information available to date for atazanavir including safety, tolerability, and efficacy.

Drug NAÏVE Population

1) Atazanavir use may be appropriate for patients initiating therapy who have a history of cardiovascular disease or multiple risk factors for cardiovascular disease where the potential worsening of LDL cholesterol may place the patient at a high risk of a clinical event. The independent risk factors for atherosclerotic cardiovascular disease (ASCVD) as referenced in the VHA dyslipidemia clinical guidelines (http://www.oqp.med.va.gov/cpg/cpg.htm) are;
   - Age (males > 45 years, females > 55 years or menopause < 40 years)
   - Family history of premature coronary heart disease; definite myocardial infarction (MI) or sudden death before age 55 in father or other male first-degree relative, or before age 65 in mother or other female first-degree relative
   - Current cigarette smoker
   - Hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg confirmed on more than one occasion, or current therapy with antihypertensive medications.
   - Diabetes mellitus (DM)
   - High-density lipoprotein (HDL) cholesterol < 40 mg/dL or LDL-C > 130 mg/mL

or

2) Patients who would likely fail any regimen administered more than once daily (QD). Patients requiring directly observed therapy (DOT), those who have failed short course(s) of twice-daily administered ARV regimens (not due to intolerance), and those who demonstrate difficulties with adhering to multi-dose per day for non-ARVs would be candidates for atazanavir. If a QD regimen is desired, then the entire regimen must use FDA approved QD agents. Since efavirenz is also approved as a QD agent, consideration should be given as to whether the patient would benefit from an efavirenz containing regimen in place of atazanavir.

Drug Experienced Population

As listed above, atazanavir has been compared with lopinavir/ritonavir alone or boosted with low dose ritonavir in drug experienced patients (including past PI exposure). In clinical trial AI424043 (single PI experienced patients), patients who received lopinavir/ritonavir showed a significantly greater fall in plasma viral load than those who received atazanavir alone. In clinical trial AI424045, the virologic response to ritonavir-boosted atazanavir was similar to that seen with lopinavir/ritonavir at study week 24. Although this is preliminary data from limited clinical trials, it suggests that atazanavir should usually be boosted with ritonavir (atazanavir 300mg QD + ritonavir 100mg QD) in patients who have already been exposed to at least one protease inhibitor containing regimen.

The standard of care in the drug experienced population includes the use of HIV resistance testing to determine the likelihood of a treatment success in a given patient. For patients who undergo genotypic testing, the presence of 3 or more historical *primary PI mutations* and/or the presence of a I50L codon change also confer likely resistance to atazanavir. Historical data may include resistance seen in different genotypes over time. When genotypic resistance testing is done, the presence of resistance to 2 or more drugs in the PI class will likely result in resistance to atazanavir. For phenotypic testing, demonstration of a three-fold increase in the concentration of drug needed to inhibit viral replication by 50% (the IC_{50}) indicates likely resistance to atazanavir. The only exception to using atazanavir in drug experienced patients with such significant resistance would be in cases of salvage where the patient has been exposed to all classes of agents and the goal of therapy is to decrease viral replication and to evolve viral strain less fit for growth in the presence of drug exposure.

Specific recommendations for atazanavir use in the drug experienced population are;

1) Patients with a documented intolerance to the current *preferred* Protease Inhibitor agents. Please refer to current version of the guidelines at http://www.aidsinfo.nih.gov/guidelines. Clinicians should consider all alternate PI class agents in conjunction with atazanavir when determining which PI is best for a given patient.

or

2) Patients clinically and/or virologically stable on an ARV regimen who are experiencing uncontrollable LDL cholesterol and/or triglycerides. Uncontrolled dyslipidemia includes patients that do not reach VHA recommended target goals with lifestyle changes and/or pharmacologic intervention. Note that the presence of a dyslipidemia is not a contraindication to using low-dose ritonavir boosting in patients receiving atazanavir, however the impact of low dose ritonavir on lipid levels is not well-described. Clinicians should continue to monitor fasting lipid levels in these patients after changing to an atazanavir regimen and both lifestyle changes and/or lipid lowering therapy may need to be continued. Clinicians are referred to the clinical practice guideline for dyslipidemias at http://www.oqp.med.va.gov/cpg/cpg.htm

or

3) Patients with documented resistance to other PI class agents where ritonavir boosted atazanavir would be expected to have activity.

II. Contraindications of atazanavir therapy

Atazanavir undergoes cytochrome p450 metabolism (CYP 3A) and can inhibit isoenzymes 3A, 1A1, 1A2, and 2C9. As such, care must be taken with co-prescribing a number of prescription products including ergot derivatives, calcium channel blockers, pimozide, midazolam, simvastatin, lovastatin, rifampin, St. John's Wort, and cisapride. As atazanavir inhibits UGT metabolism, irinotecan and indinavir should not be used with atazanavir. Clinical trials data for the combination of atazanavir *plus* saquinavir demonstrated inferior virologic response in a PI experienced population and thus this combination should not be prescribed. When used with efavirenz, atazanavir should be prescribed in a boosted format (atazanavir 300mg QD + ritonavir 100mg QD) with normal dose efavirenz. No data are available on the co-administration of atazanavir with nevirapine but history with other PI class agents suggests that ritonavir boosting may be required. Tenofovir lowers non-boosted atazanavir AUC and C_{min} by 25% and 40% respectively while it lowers these pharmacokinetic parameters by 25% and 23% when boosted with ritonavir. Clinicians should prescribe boosted atazanavir when co-prescribed with tenofovir until more information is known about this interaction. Atazanavir solubility decreases as pH increases. Reduced plasma concentrations of atazanavir are expected if antacids, buffered medications, H_2-receptor antagonists, and proton pump inhibitors are administered with atazanavir.

III. Clinical Response Follow up

Clinical follow up of virologic response to an atazanavir-containing regimen should be tailored for each patient. This includes monitoring CD4+ lymphocyte counts, HIV viral load, and performing the appropriate safety laboratory tests relative to the ARV backbone, co-morbid disease, and co-administered medications prescribed to the patient. The clinician and patient should make the decision of when atazanavir therapy should be stopped secondary to intolerance, adverse events, clinical or virologic failure.

IV. Cost of Therapy

This cost analysis only includes the impact of using a DHHS defined *preferred agent* versus atazanavir (e.g. does not include the other costs associated with the ARV backbone). When compared to the nRTI class agent efavirenz, the cost of using atazanavir in place of efavirenz adds $246.33 per 30-day supply to the ARV backbone regimen. Although from different classes, these two agents showed virologic and immunologic equivalency in the drug naïve population. If the cost of atazanavir is compared to the current DHHS preferred PI class agent (lopinavir/ritonavir), the added cost of prescribing atazanavir in place of lopinavir/ritonavir is $99.12 per 30 day supply. A more fair comparison within the same PI class would be between ritonavir boosted atazanavir with lopinavir/ritonavir. A price comparison between these two boosted drugs results in an added cost of $133.18 per 30 day equivalent supply. As mentioned previously, the estimation of costs potentially associated with dyslipidemias associated with ARV therapy which may or may not occur with long-term atazanavir therapy can not be currently be factored into a cost effectiveness model.

References

DHHS Guidelines - http://www.aidsinfo.nih.gov/guidelines/

Pharmacokinetics

Mummaneni V, Randall D, Chabuel D et.al. Steady-State Pharmacokinetic (PK) Interaction Study of atazanavir (ATV) with Clarithromycin (CLR) in Healthy Subjects. 42nd ICAAC Abstracts, American Society for Microbiology, September 27 - 30, 2002, San Diego, CA, Poster H-1717

Agarwala S, Russo R, Mummaneni V et.al. Steady-State Pharmacokinetic (PK) Interaction Study of atazanavir (ATV) with Ritonavir (RTV) in Healthy Subjects. 42nd ICAAC Abstracts, American Society for Microbiology, September 27 - 30, 2002, San Diego, CA, Abstract: H-1716

O'Mara E, Agarwala S, Randall D. Pharmacokinetic Interaction Study of Atazanavir (ATV) with Efavirenz (EFV) and Ritonavir (RTV). 42nd ICAAC Abstracts, American Society for Microbiology, September 27 - 30, 2002, San Diego, CA, Abstract:

Tenofovir-Atazanavir interaction – BMS FDA filing for studies AI454-181 and PUZZLE 2 (ANRS 107).

Clinical Trials

Sanne I, Piliero P, Squires, K et.al. Results fo a Phase 2 Clinical Trial at 49 Weeks (AI424-007) A Dose-Ranging, Safety, and Efficacy Comparative Trial of Atazanavir at Three Doses in Combination with Didanosine and Stavudine in Antiretroviral-Naïve Subjects

Murphy R, Pokrovskiy V, Rozenbaum W, et.al. Long-Term Efficacy and Safety of Atazanavir (ATV) with Stavudine 9d4T) and Lamivudine (3TC) in Patients Previously Treated With Nelfinavir (NFV) or ATV: 108-Week Results of BMS Study 008/044 10th Conf Retro and Opp Infections. Boston. 2003. Poster G1-36

Squires KE, Giordano M, Sension M et.al. Atazanavir (ATV) QD vs Efavirenz (EFV) QD with Fixed –Dose Zidovudine (ZDV) and Lamivudine (#TC) BID: Comparison of Antiviral Efficacy and Safety 48-Week Results from BMS AI424-034 Phase III Pivotal Study. 42nd Interscience Conf Antimicro Agents and Chemo. Sept 27-30. 2002. San Diego CA Poster H-1076

Badaro R, DeJesus E, Lazzarin A et al. Efficacy and safety of atazanavir (ATV) with ritonavir (RTV) or saquinavir (SQV) *versus* lopinavir/ritonavir (LPV/RTV) in combination with tenofovir (TFV) and one nRTI in patients who have experienced virologic failure to multiple HAART regimens. 2nd IAS Conf on HIV Pathogenesis and Treatment, Paris July 2003 Abst 118

Safety

Sension M, Squires K, Cahn P et al. change in Total Cholesterol (as per NCEP ATP III) From Baseline at 48 weeks Following Treatment with Atazanavir (ATV) or Comparator Protease Inhibitors (PIs) 40th Meeting of the Infectious Diseases Society of America. Oct 24-27, 2002. Chicago IL Poster 468

Cahn P, Piliero P, Giordano M et.al. Atazanavir (ATV): Antiretroviral Efficacy in HIV-infected Patients co-Infected with Hepatitis B and/or C Viruses (Hep B, Hep C). 42nd Interscience Conf Antimicro Agents and Chemo. Sept 27-30. 2002. San Diego CA Poster H-1730

Resistance

Colonno RJ, Thiry A, Limoli K, and Parkin N. Activities of Atazanavir (BMS-232632) against a Large Panel of Human Immunodeficiency virus type 1 clinical isolates resistant to one or more approved protease inhibitors. Antimic Agents Chemother. 2003:47(4):1324-1333

Prepared by: Larry Mole, PharmD.

Reviewed by: Matt Goetz, MD, Chief, Infectious Diseases, VA Greater Los Angeles Healthcare System, Public Health Strategic Health Care Group (PHSHG), and the HIV Treatment Advisory Panel