Atazanavir (BMS-232623), brand name Reyataz®

NDA 21-567 and 21-568

To lipid it or not to lipid it

by Rob Camp

INTRODUCTION

Atazanavir (ATV) is an azapeptide protease inhibitor under development by Bristol-Myers Squibb, licensed from Novartis. Overall, the drug looks virologically similar to nelfinavir (NFV) in phase II/III clinical trials, with fewer effects on lipids.

Atazanavir should be taken with a "light meal." It is available orally as 100mg, 150mg and 200mg capsules, and as a powder that can be mixed with juice or milk. Capsules should be stored at room temperature, 15-30 C (59-86 F).

Atazanavir is being reviewed as a protease inhibitor (PI) for people with HIV starting their first treatment regimen with a PI. That is where it will have best effect as an unboosted PI. If resistance to other PIs is present, ATV will probably lack potency as a single PI due to cross-resistance. It is being investigated with a 100 mg ritonavir booster, although no data on this combination have yet been published. Pharmacokinetic studies indicate that ATV 300/r100 is at least as good as ATV 400.

Based on data from ongoing and completed studies, specifically the 008, 009, and 034 studies, TAG and the undersigned organizations believe that the FDA should approve the Bristol-Myers Squibb application for accelerated approval of Reyataz® brand atazanavir (NDA 21-567 and 21-568) to treat HIV infection in combination with other antiretroviral agents in adults, provided that the follow up studies recommended below are commenced and successfully completed in a timely fashion.

- Dosing: comparing 400mg QD with 600 & 800 mg.
- Switch studies to ATV from other PIs, efavirenz and nevirapine.
- Drug-drug interaction/PK studies with methadone, H2 blockers, rifampin, statins, fibrates, ribavirin, efavirenz, nevirapine, tenofovir, fosamprenavir, saquinavir (Invirase and Fortovase), and pegylated interferon.
- Pediatric studies to determine safe and effective dose regimens.
- Studies to determine the significance of ATV-associated changes in QT intervals.
- Further studies of hyperbilirubinemia and ATV's effect on people with compromised liver function.
- Long-term safety studies.
- Studies to determine the impact of ATV + ritonavir on lipid levels and CVD risk factors.
- Resistance studies, including the relationship between the I50L mutation and potential hypersusceptibility to other PIs.
- Studies in PI-pretreated individuals, comparing ATV/r to lopinavir/r and other second line and salvage regimens.

OVERVIEW

This paper will discuss the following issues:

1. Executive Summary

ATV is the first protease inhibitor that can be used once daily without using ritonavir or any other cytochrome P450 inhibitors as boosters, although there may be situations (second-line, high viral loads, etc.) where boosting it with 100 mg of ritonavir (/r) may be useful. Current data only support its use as a first-line single PI in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs). Data on ATV/r, and its supposed lipid effects, need to be generated and shared in second-line and subsequent regimens.

The 48-week virologic efficacy of ATV is similar to that of nelfinavir - and in BMS 034 it showed comparable efficacy to that of efavirenz, though in most previous studies EFV was more potent than it appeared here - as a first line regimen. While ATV can thus be approved as a first line PI, but data are insufficient to recommend use of ATV as a sole PI in those who have already failed another PI-containing regimen. The label should clearly state that un-boosted, ATV has only been studied as a first-line PI.

The safety profile so far is not alarming, although concerns about hyperbilirubinemia and hepatic issues need to be more clearly addressed in ongoing studies. For those with mild liver impairment, are dose reductions to 300mg recommended? What about the dose for more serious liver problems? Although there may be no difference between hepatitis co-infected and non-co-infected people with hyperbilirubinemia, ATV should be used with caution (i.e., more visits and laboratory analyses) by people with abnormal LFTs at baseline, including those with chronic hepatitis. Sadly, the serious adverse events collected in the expanded access program have not been categorized or published to help define the risks of ATV use. This should be done immediately.

The 008/044 study showed that switching from NFV to ATV is a viable strategy to reduce elevated lipids, suggesting that switching from any non-virologically failing regimen to ATV can be done safely.

Contrary to initial findings, ATV shares cross-resistance with most other protease inhibitors. It is unlikely to be of any use when more than five common protease gene mutations are present.

Interaction studies show that efavirenz lowers ATV absorption by 70%, so this combination is only recommended with a ritonavir booster. What are the effects on lipids of ATV/r 100? **ATV/r is recommended by the sponsor after any PI failure. We need a study in people who experience previously single and multiple PI failure.**

For absorption, ATV is best taken with "food". What kinds of food were used, and how much was recommended? Absorption was less with a high-fat meal. During studies, how were patients advised? Food studies and guidelines are needed.

This drug was heavily studied in South Africa, five countries in South America, and two in Asia. We hope that BMS makes this drug as accessible in these countries as in developed nations but at a lower price.

In summary, ATV has both pros (the lipid profile) and cons (hyperbilirubinemia), and with the right clinical use, it is clearly a welcome addition to the panoply of drugs now available. The undersigned community members support accelerated approval. Before full approval is granted, the community believes the following studies must be done:

2. Follow Up Studies That Must Be Done

Studies that need to be done include the following:

Dosing. Is the chosen dose the optimum dose? 400 mg QD provides a low inhibitory quotient. It is not altogether clear why BMS chose the 400 mg QD dose for its Phase III trials. Other studies needed: dosing of 600 mg vs. 800 mg vs. 400/100 as initial therapy, etc.

Switch studies. Because many people with high lipids are going to be interested in switching to ATV, it should be clearly demonstrated that this can be done safely and with no loss to efficacy of the regimen in the long term.

Drug-drug interaction/PK studies. Interaction studies need to be done with methadone, H2 blockers, rifampin, statins, fibrates, ribavirin, efavirenz, nevirapine, tenofovir, fosamprenavir, saquinavir (Invirase and Fortovase), and pegylated interferon.

Pediatrics. No data have been generated for pediatric use. PACTG 020 is presently accruing patients.

Cardiovascular (CV) safety. ATV affects the QT interval, like lopinavir/ritonavir. The clinical significance of ATV-associated changes in cardiac electrical impulses should be defined, especially with multi-PI regimens.

Liver safety. ATV may be contraindicated in people with a history of hyperbilirubinemia or other hepatic abnormalities. Further studies need to be undertaken to characterize ATV's side effects in these people, and where and when atazanavir may be contraindicated.

Long-Term Safety.

Metabolics - to measure the effect on CV risk factors (with or without ritonavir) and the insulin resistance.

Resistance - Does I50L clinically mean hypersusceptibility to other PIs? Under what circumstances? A study is needed.

PI-experienced persons. ATV/r is recommended after any PI failure by BMS. We need a clinical study similar to the lopinavir/ritonavir vs. ATV study, in single or multi-failure people with ATV/r before this can be recommended clinically for PI failures.

3. Pre-Clinical Data

So called "first generation" HIV protease inhibitors are large molecules, and as such, large doses are needed daily to maintain efficient concentrations in plasma. Azapeptides are smaller and may have longer half lives in the body and blood.

What is an azapeptide? Peptides, which make up proteins, are composed of amino acids lined up in a chain. In azapeptides the a-carbon replaces a nitrogen atom. This confers a more stable conformation as well as resistance to degradation by many proteolytic enzymes. Some marketed azapeptide drugs include angiotensin II, oxytocin, and LHRH (Zoladex® for prostate cancer).

Atazanavir displays significant activity against laboratory and primary HIV-1 isolates in cell lines and primary peripheral blood mononuclear cells (PBMCs), and is non-genotoxic, and non-teratogenic in rats and rabbits.

4. Pharmacokinetics & Dosing

In an early single-dose Phase I, placebo-controlled, double-blinded study in HIV-negative males at five doses (100, 300, 600, 900, & 1200 mg), atazanavir pharmacokinetics (PK) were similar to other azapeptides, with rapid absorption and slow elimination. The relative bioavailability was 57-80% and the pharmacokinetic profile made once daily dosing feasible. The PK profile seemed favorable (300 mg yielded plasma levels above the EC50).

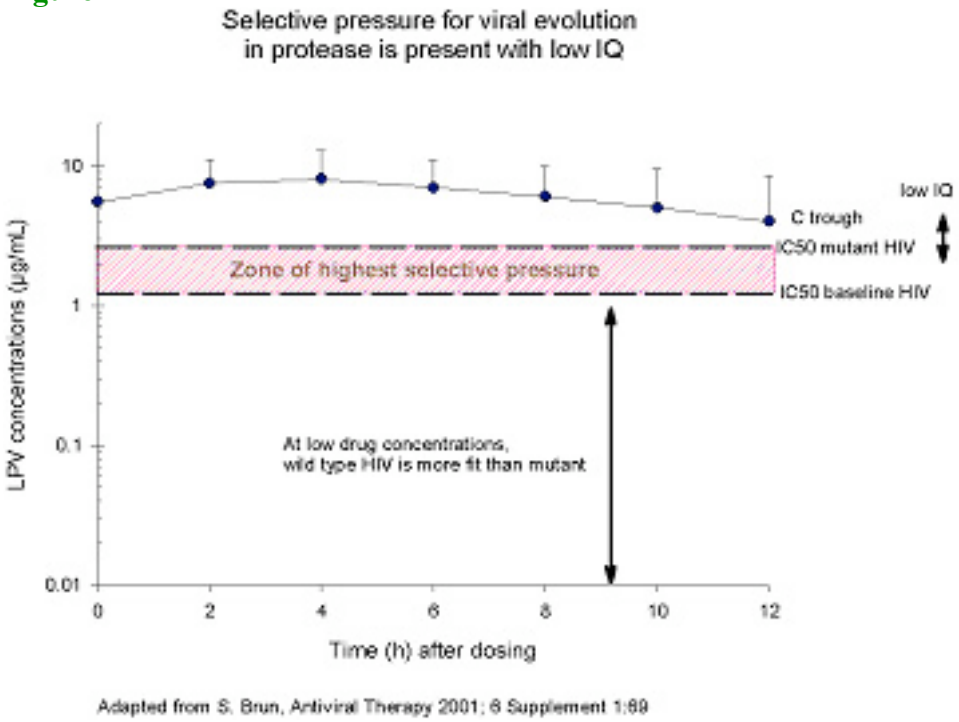
Administration of atazanavir following a light meal resulted in an increase in both mean peak plasma concentration (Cmax) and mean area under the curve (AUC) vs. administration with either a high-fat meal or in a fasting state. For doses above 300 mg, plasma concentrations remained above EC50 values for more than 24 hours, supporting once-daily dosing.

5. Inhibitory Quotient (IQ)

The inhibitory quotient is a model for understanding and evaluating drug pharmacology, including both pharmacokinetics and the potential development of resistance. IQ is the ratio between the minimum drug concentration (Cmin, the "trough") and the 50% or 90% inhibitory concentration (IC50 or IC90). Figure 1 illustrates this concept with lopinavir: the 50% inhibitory concentration (IC) is well below the drug's trough concentrations. In other words, the minimal concentrations are well above the concentrations needed to inhibit virus replication. When HIV susceptibility to lopinavir diminishes, higher drug concentrations are required to inhibit HIV (Figure 2).

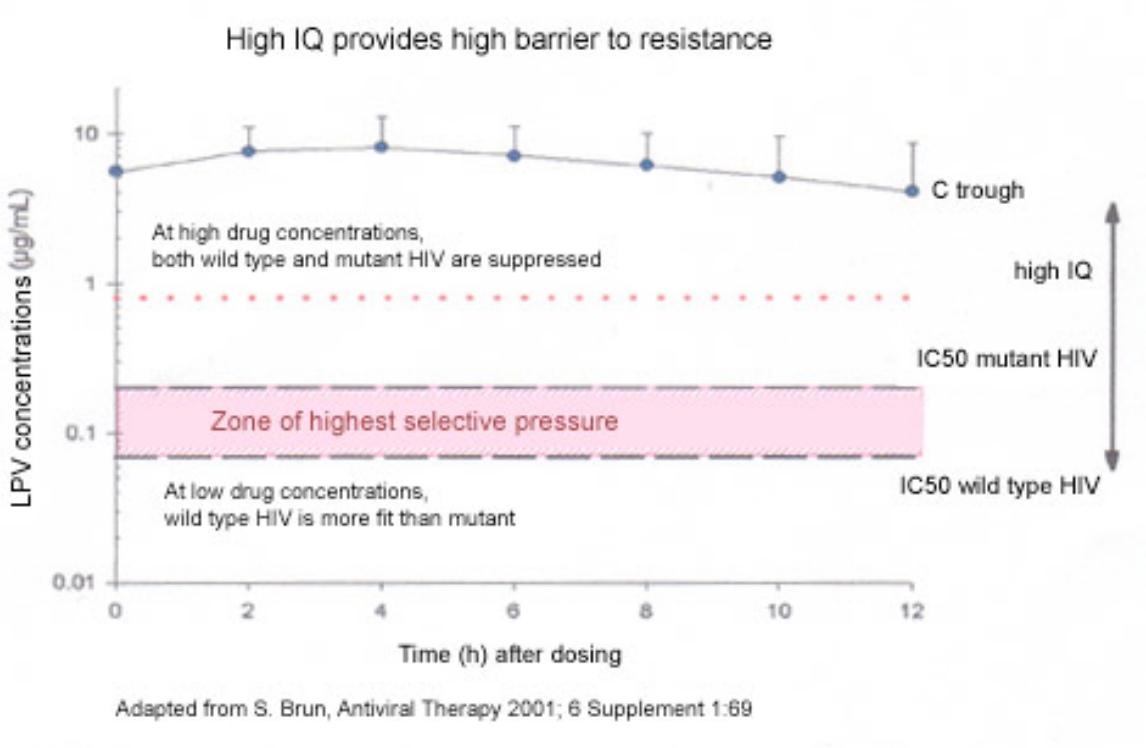
When trough concentrations are lower than what is necessary to block HIV replication, HIV will continue replicating. The higher the IQ of a drug in a regimen, the more solid its barrier against resistance.

Figure 1



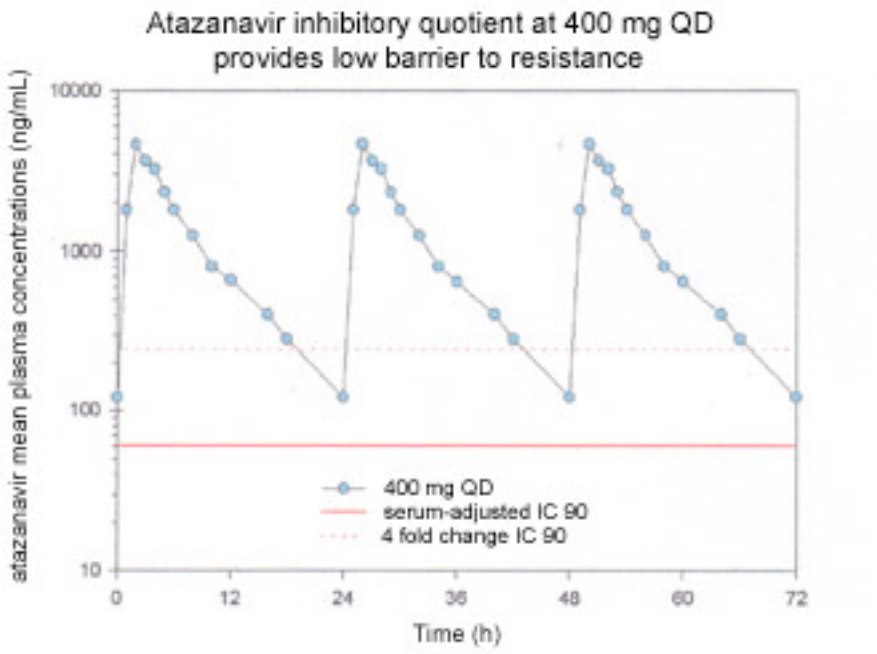
Adapted from S. Brun, Antiviral Therapy 2001; 6 Supplement 1:69

Figure 2



Figures 3 and 4 show a simulation of three consecutive days of atazanavir dosing (based on phase I /II studies), and dose effects on plasma PK levels at 24 hours in relation to the IC90 of wild-type HIV and HIV with four-fold reduced susceptibility to ATV.

Figure 3

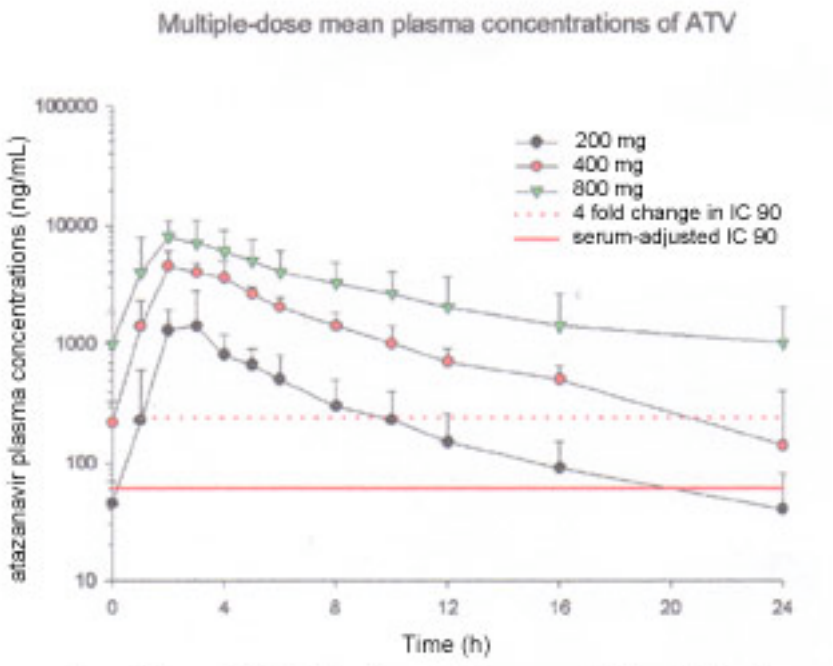


From Mummaneni et al, 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; Sept. 27-30th 2002, San Diego

As shown in Figure 4, 200 mg QD is clearly sub-optimal, as after 12 hours, levels are below the adjusted IC90 (concentration able to inhibit 90% of virus replication adjusted for serum protein binding). At 800 mg QD, trough levels are above wild type IC90 and virus replication is theoretically controlled. At 400 mg QD, drug concentration is above the adjusted IC90 most of the time, but the inhibitory quotient is low, reducing the barrier to resistance.

To further illustrate this low resistance barrier, an HIV strain with some level of resistance (four fold change in susceptibility, as indicated by the upper dotted line), would not be controlled by atazanavir. Unlike lopinavir, where a four-fold change in susceptibility probably does not alter its ability to control HIV replication, a change of the same magnitude for atazanavir may reduce its efficacy. This more resistant HIV variant would be exposed to inhibitory concentrations 75% of the time at 400 mg QD. For such variants, higher doses would be preferable. During the period where plasma concentrations are below the IC90, replication can start again. Based on the IQ, a 600 mg QD dose may have been more efficacious in controlling HIV replication.

Figure 4



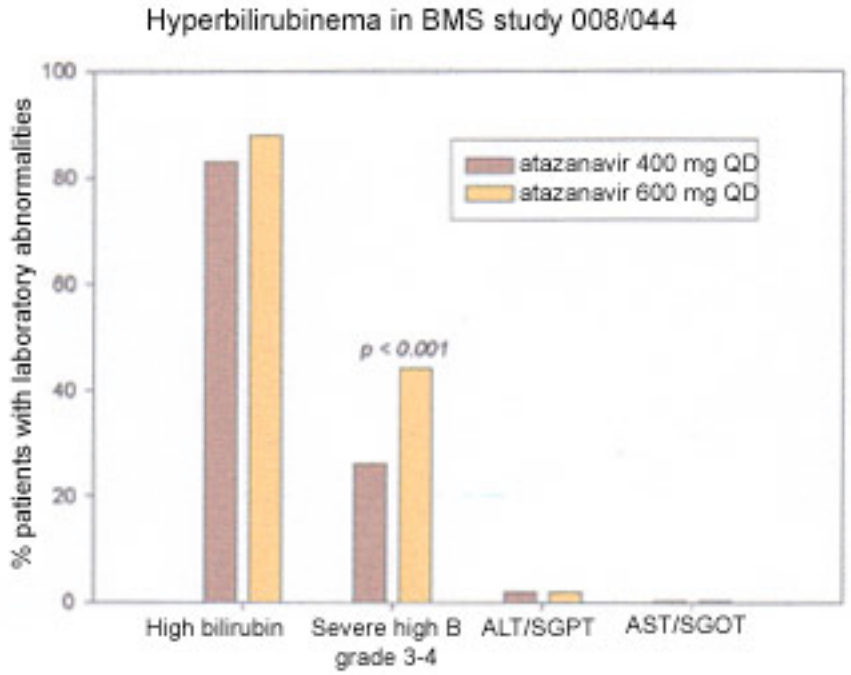
From O'Mara et al. 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; Sept. 27-30th 2002, San Diego. Abstract H-1717

BMS vacillated between 400 and 600 mg QD for its pivotal licensing studies. A limiting factor might be the laboratory abnormalities reported with atazanavir over time, mainly hyperbilirubinemia. This is probably the reason why the final 400 mg QD dose was chosen. This dose may be modified when ATV is co-administered with liver cytochrome inducers or inhibitors, like efavirenz or ritonavir respectively, although data at this time are minimal and no recommendations can be made.

6. Safety & Side Effects

The manufacturer states that it chose the 400 mg dose due to similar efficacy and reduced toxicity, particularly hyperbilirubinemia. But in the 008/044 study, the overall incidence of AEs was comparable between the ATV 400 mg (93%) and ATV 600 mg (95%) treatment arms. The long-term safety profile of ATV-treated patients was consistent with that observed for study 008 alone. Jaundice was reported more frequently in the ATV 600 mg than in the ATV 400 mg treatment arm (22% vs. 13%). The incidence of scleral icterus and scleral jaundice was comparable between the two arms.

Figure 5



Unconjugated bilirubinemia. Hyperbilirubinemia is an excess of bilirubin in the blood. It occurs as a result of liver or biliary tract dysfunction or with excessive destruction of red blood cells and is classified as conjugated or unconjugated (direct or indirect), according to the type of bilirubin present. Jaundice is manifested when excess bilirubin is deposited in the skin and mucous membranes.

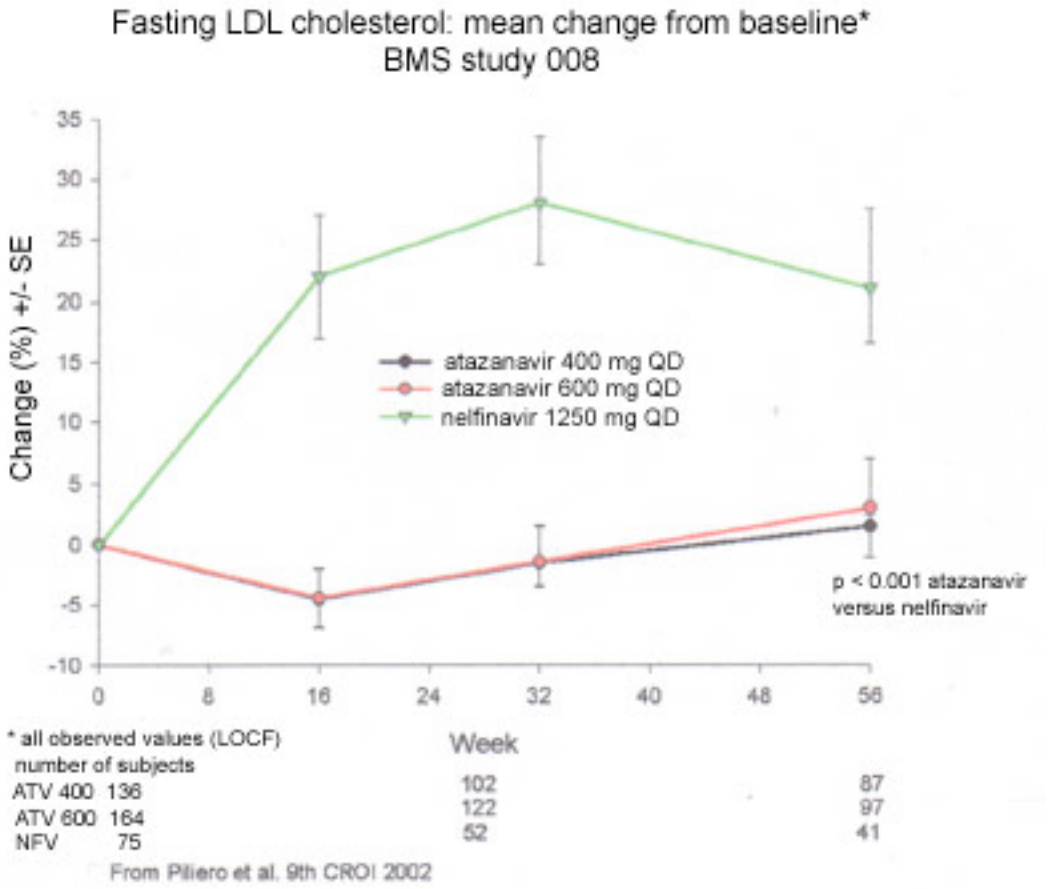
As many as 35% of persons treated with atazanavir experience primarily unconjugated bilirubinemia increases, with jaundice and/or scleral icterus (yellowing of the eyes) in at least 6% of patients. This seems dose-related, as shown in Figure 5 above.

Unconjugated hyperbilirubinemia seen with atazanavir therapy has been reported as mild, and has appeared within the first several days to one week of initiation of therapy. The elevated bilirubin levels seem not to have health consequences and resolve soon after discontinuation of the drug. The hyperbilirubinemia seen with ATV is similar to that seen in people on indinavir, which occurs in approximately 10% of IDV users and includes yellowing of the skin and/or eyes. IDV is contraindicated with ATV.

One problem may occur for people who experienced hyperbilirubinemia due to hepatitis C, or other drug-related (IDV) toxicity. Is ATV safe for people with pre-existing liver disease? The sponsor states that ATV-associated bilirubinemia is not related to increased transaminases, nor is it more frequent in those coinfected with HCV or HBV. This needs to be documented in those with mild to moderate fibrosis (METAVIR F0 - F2 or Knodell HAI 0 or 1). In severely liver impaired people, a dose reduction is recommended due to reduced ATV clearance. Such individuals may want to consider avoiding or reducing alcohol intake.

Lipid profiles. Phase II studies 007 and 008 compared various atazanavir doses (200, 400 or 600 mg QD) to nelfinavir, a moderately potent first-line protease inhibitor, with two nucleoside analogues as background. CD4 lymphocytes and HIV viral load responses were similar. The main difference was seen in lipid-related measurements: total cholesterol, LDL cholesterol, and fasting triglycerides. In Figure 6, LDL cholesterol in the 008 study is almost unchanged after more than a year of ATV in naive patients, while it increased by 23% in the nelfinavir group (P<0.001).

Figure 6



BMS conducted 008/044, a switch study from nelfinavir to atazanavir over the same background regimen (d4T and 3TC). The idea was to explore the lipid profile after the atazanavir switch. The nucleoside analogues were left unchanged. For this study, patients either continued treatment (if on atazanavir) or switched to atazanavir 400 mg QD. Baseline characteristics were similar to the 007 study: most subjects were white (55%) and male (63%). The median age was 34 years. The median HIV RNA level was 4.74 log10 c/mL, and the median CD4 cell count was 270 cells/mm3.

For the switched cohort, total cholesterol significantly decreased by 16% at week 24, HDL cholesterol increased by 6%, fasting LDL cholesterol decreased by 20% and fasting triglycerides decreased by 25%. For the switched people, statistically significant mean

percent changes in TC (-16%, P<0.0001), HDL-C (+5%, P<0.05), fasting LDL-C (-21%, P<0.0001) and fasting TG (-28%, P<0.0001) were observed to Week 12. For all lipid parameters except HDL-C, these statistically significant differences were maintained through Week 24.

Hematuria. Another adverse effect that has been observed in people in studies is microscopic hematuria, a presence of red blood cells (RBCs) in the urine, first seen in study 005. In people with renal insufficiency, closer monitoring may be advised. In microscopic hematuria, the urine appears normal to the naked eye, but examination under a microscope shows a high number of RBCs.

Treatment for hematuria depends on the cause. If no serious condition is causing the hematuria, no treatment is necessary. It may be wise to stop the atazanavir to ascertain whether or not it is the culprit.

Uric acid crystals were also observed in some urine samples.

The idiopathic abdominal pain seen in about 5% of people in the ATV arms of all studies needs to be better defined.

With these many side effects, we must highlight the need for attentive pharmacovigilance, which can pick up less frequent problems, or other problems not seen until much later.

7. Resistance Profile

Pre-clinical work suggested that atazanavir might demonstrate a distinct resistance profile. But the amino acid changes associated with ATV resistance overlap with other protease inhibitors, with the exception of the I50L and N88S mutations. The pathways to atazanavir resistance vary, but appear to involve the N88S. As such, cross-resistance is expected.

A better sense of the resistance profile in antiretroviral-experienced people could have been achieved through a closer look at the virologic outcome of ATV use in the expanded access program (EAP).

Resistance in naïve people

The I50L mutation does not confer cross-resistance to other PIs as assessed by in vitro changes in susceptibility. Indeed, susceptibility to other PIs may be increased ("hypersusceptibility"). At this time, no clinical relevance can be extrapolated. Only a handful of samples have been isolated and phenotyped. More studies here are needed. This hypersusceptibility differs from what is seen with mutations I50V or D30N associated with amprenavir and nelfinavir.

Resistance in PI treatment-experienced people

Seven amino acid substitutions were identified that correlated with decreased susceptibility to ATV: two primary (82 & 90) and five secondary (10, 20, 46, 54 & 73) residues. While no single substitution was uniquely predictive of reduced ATV susceptibility, the presence of at least five of the seven key substitutions correlated strongly with an ATV fold-change greater than four-fold among PI resistant clinical isolates, which as previously stated, is detrimental to a constant maintenance of drug above the IC90.

One possible combination to study would be ATV/r + AMP in salvage settings, as only either the I50L or I50V will be selected. This may force the virus down a pathway that will make it very susceptible to the other PI(s).

8. Efficacy

Phase II, Comparison to nelfinavir

BMS studies 007 and 008 compared 693 people on atazanavir to 194 on nelfinavir. There was no significant difference in the proportion of patients achieving ≤400 or ≤50 HIV-RNA copies/mL at week 48. CD4 lymphocyte increases were similar, approximately 300 CD4 cells from baseline.

Table 1: 48 Week Results: ATV vs. NFV in BMS 007/008

	CD4 increase	*HIV RNA <400 (%)*	*< 50 (%)*
ATV 400	+293	80	58
ATV 600	+300	82	54
NFV»ATV	+310	86	59

Phase III, Study 034: Comparison to efavirenz

In the 034 study, treatment-naive patients treated with atazanavir (ATV) or efavirenz (EFV) based regimens plus 3TC/zidovudine (ZDV) achieved comparable efficacy at 48 weeks. Of the 805 patients, 82% completed 48 weeks of treatment. Switching was not permitted. An intent-to-treat analysis showed that 70% of ATV and 64% of EFV patients had viral loads below 400 copies/mL; and, 32% of ATV and 37% of EFV patients had viral loads below 50 copies/mL. The rise in CD4 counts was 176 for ATV and 160 for EFV treated patients.

Note: While there was no statistical difference between the two arms, it is unclear why the control arm (3TC + ZDV + EFV) performed so poorly, compared to many earlier studies, in which approximately 70% of patients achieved viral loads below 50 copies/mL. One theory for this that must be proven is that the analysis undertaken was too strict, i.e., one blip above 50 to be considered a failure, even if the person went undetectable again at the next analysis.

Table 2: Efficacy, Safety & Tolerance of ATV vs. EFV in BMS 034			
	Atazanavir	*Efavirenz*	*p-value*
N	404	401	
Week 48 efficacy changes			
HIV RNA<50	70%	64%	?
HIV RNA<50	32%	37%	?
CD4 gain	+176	+160	?
Toxicity			
Diarrhea	5 (1%)	10 (2%)	NS
Nausea	57 (14%)	51 (31%)	NS
Rash	25 (6%)	41 (10%)	<0.05
Headache	23 (6%)	25 (6%)	NS
Dizziness	8 (2%)	24 (6%)	<0.01
Vomiting	17 (4%)	27 (7%)	NS
Jaundice	21 (5%)	0	<0.001
Scleral icterus	6 (1%)	0	<0.05
Week 48 metabolic changes			
Total cholesterol	+2%	+21%	<0.05
LDL cholesterol	+1%	+21%	<0.05
HDL cholesterol	+13%	+24%	NS
Triglycerides	-9%	+23%	<0.05

Atazanavir in salvage regimens

The Puzzle study. Individuals with HIV-RNA > 10,000 copies/ml, after failure of two PIs and one NNRTI, were treated with atazanavir 300 mg QD / ritonavir 100 mg QD, tenofovir 300 mg QD and reverse transcriptase inhibitors.

Tenofovir (TDF) decreases atazanavir AUC by 25.2% (p=0.05, reported NS) and ritonavir (RTV) AUC by 25.6% (p=0.05, reported NS) after four-weeks of TDF. One explanation offered was that TDF lowers RTV, which lowers ATV. As TDF is a widely used new drug, better studies are needed to confirm this and ascertain its clinical significance. Clearly, when the combination of ATV + TDF is used, the ATV should be boosted by RTV.

Atazanavir + saquinavir QD. BMS study 009 evaluated the safety, tolerability, and efficacy of dual PI therapy with atazanavir (400 or 600 mg qd)/saquinavir (1200 mg qd), or ritonavir (400 mg BID)/saquinavir (400 mg BID) + 2 nucleoside reverse transcriptase inhibitors (NRTIs) after virologic failure on a prior regimen. This was a randomized, blinded study in 85 adults with HIV RNA 1,000-100,000 copies/mL and CD4 <150 cells/mm^3. The ritonavir/saquinavir regimen was more potent but had more discontinuations for treatment-related adverse events, as shown here in Table 3 (P-values did not reach significance):

Table 3: 48 Week Results on ATV/SQV QD vs. RTV/SQV BID in BMS 009			
	ATV/SQV QD		*RTV/SQV BID*
	400 mg	*600 mg*	
N	34	28	23
HIV RNA log_{10} c/mL	-1.44 (0.25)	-1.19 (0.22)	-1.66 (0.23)
CD4 cells/mm^3	109 (24)	55 (26)	149 (36)
ADE requiring treatment discontinuation	3 (9%)	3 (11%)	7 (30%)

9. Drug-Drug Interactions

Atazanavir and efavirenz/r

Efavirenz (EFV) lowers ATV 400 mg exposure by approximately 70% when ATV is unboosted.

When administered with ritonavir, atazanavir Cmin is increased approximately ten-fold above that observed without ritonavir, while the AUC and Cmax are increased 3.3- and 1.8-fold, respectively. This augmented exposure appears to permit atazanavir and efavirenz co-administration. The recommended combination dosage is ATV 300 mg /r 100 mg + EFV 600 mg, all QD. Both FDA and the European Medicines Evaluation Agency (EMEA) have asked BMS for specific ATV and RTV interaction data. The combination of ATV and RTV would probably negate the primary reason for using ATV, its favorable lipid profile.

There is growing interest in other NRTI-sparing alternatives. A similar study with nevirapine is being discussed with the FDA and the EMEA (although NVP QD is under scrutiny after the 2NN study results).

Other drugs

Coadministration of atazanavir and saquinavir (soft-gel capsules) with a high-fat meal resulted in a 4- to 7-fold increase in saquinavir AUC.

Coadministration of atazanavir and rifabutin resulted in a two-fold increase in rifabutin AUC. A dosage reduction of rifabutin is recommended.

Diltiazem, a calcium-channel blocker, is used to treat high blood pressure and to control chest pain (angina). Coadministration of atazanavir and diltiazem resulted in a two-fold increase in diltiazem AUC; a dosage reduction of diltiazem is recommended.

Coadministration of atazanavir and clarithromycin resulted in a 1.9-fold increase in clarithromycin AUC and a 30% increase in atazanavir AUC; a dosage reduction of clarithromycin is recommended.

Coadministration of atazanavir and ketoconazole, a potent inhibitor of CYP3A4, resulted in an 11% increase in atazanavir AUC; no dose adjustment is recommended.

Atenolol is a beta-blocker used for hypertension, myocardial infarction, arrhythmias, and angina. Coadministration of atazanavir and atenolol resulted in a 25% increase in atenolol AUC. No dose adjustment is recommended.

Ortho-Novum (ON 777) is a combination oral contraceptive of ethinyl estradiol and norethindrone. Surprisingly, some major interactions were seen with ON 777, but no action was recommended. ATV 400 increases norethindrone by 110% (AUC) and ethinyl estradiol by 48%. Although there were no deaths, three of 22 women discontinued the study, and >10% of women had vomiting, constipation, scleral icterus, and increased bilirubin (grades 1 or 2). BMS concluded, "no dose adjustment is recommended".

There were no clinically significant effects on AUC and no dosage adjustment was necessary when atazanavir was administered concomitantly with zidovudine, lamivudine, or stavudine.

10. Expanded Access Program

Patients eligible for inclusion into the EAP are those over 16 years of age who have virologic failure due to resistance, intolerance and/or adherence problems with current HIV medications; or have multiple toxicities or intolerance to their HIV medication without virologic failure; or have severe elevated lipids in the blood (e.g., cholesterol, triglycerides) that do not respond to lipid-lowering medication.

Restrictions apply regarding the use of ATV with certain potentially contraindicated drugs. Patients are excluded for any of the following reasons: 1) pregnancy or breast-feeding, 2) elevated liver enzymes (a majority of HIV/HCV co-infected people are not eligible), 3) significant cardiovascular disease, or 4) other restrictions as indicated in the protocol, including a restriction on those with a high alcohol intake.

It started in May 2002 and now has approximately 3000 people enrolled in more than 25 countries. SAEs have not been reviewed. **Once again, an EAP has been under-utilized as far as getting useful real-life information.**

The following organizations and individuals have signed on to this paper along with Treatment Action Group:

[list in formation]

- AAPNW (AIDS Action Project Northwest), Portland, Oregon
- AIDS Action Baltimore
- AIDS Treatment Activists Coalition
- AIDS Treatment Data Network, New York, New York
- Being Alive, Long Beach, California
- The Center for AIDS, Hope & Remembrance Project, Dallas, Texas
- CHAMP (Community HIV/AIDS Mobilization for Power), Philadelphia, Pennsylvania
- Gay Men's Health Crisis (GMHC), New York, New York
- IFARA (International Foundation for Alternative Research in AIDS), Portland, Oregon
- Positives For Positives, Cheyenne Wyoming
- Program for Wellness Restoration, PoWeR, Texas
- Carlton Hogan, University of Minnesota
- Melvin Littles, New York, New York
- Robert J. Munk, Arroyo Seco, New Mexico
- Tracy Swan, New York, New York

References

Becker SL, The pharmacology of atazanavir, 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Diego, 27-30 September 2002.

Benson C, Schooley R, Williams W. Study 005; Substudy 006; Substudy 007; 008, Safety and effectiveness of a three-drug combination treatment for recently infected or converted HIV patients, National Institute of Allergy and Infectious Diseases (NIAID), Bristol-Myers Squibb.

Colonno RJ, Thiry A, Parkin NT. Amino acid substitutions that correlate with decreased susceptibility to atazanavir and other HIV-1 protease inhibitors. Abstract H-2049, 42nd ICAAC, San Diego, 27-30 September 2002.

Colonno R, Rose R, Cianci C, et al. Emergence of atazanavir resistance and maintenance of susceptibility associated with a I50L substitution in HIV protease. Abstract 597,10th CROI, Boston, February 2003.

Condra JH, Petropoulos CJ, Ziermann R, et al. Drug resistance and predicted virologic responses to human immunodeficiency virus type 1 protease inhibitor therapy. J Infect Dis 2000, 182:758-765 [erratum J Infect Dis 2001, 183:993-994].

Durant J, Clevenbergh P, Garraffo R, et al. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradapt study. AIDS 2000, 14:1333-1339.

Eron JJ, "Title", abstract no, 42nd ICAAC, Sept 27-30, 2002

Freedman BI, Soucie JM, et al. Familial clustering of end-stage renal disease in blacks with HIV-associated nephropathy. Am J Kidney Dis 1999 Aug;34(2):254-8.

Lazdins JK, Mestan J, Goutte G, et al. In vitro effect of a1-acid glycoprotein on the anti-human immunodeficiency virus (HIV) activity of the protease inhibitor CGP 61755: a comparative study with other relevant HIV protease inhibitors. J Infect Dis 1997, 175:1063-1070.

Lin F, Gong YF, Robinson BS, et al. Resistance profile of BMS-232632, a new inhibitor of HIV protease. Abstract 18, 3rd International Workshop on Drug Resistance and Treatment Strategies, San Diego, 1999.

Miller BF, Eoyang (eds.). Miller-Keane Encyclopedia & Dictionary of Medicine, Nursing, & Allied Health. 6th Edition. WB Saunders, 1997.

Murphy R, Ledesma E, et al. A nelfinavir (NFV) to atazanavir (ATV) switch correlates with lipid improvements at 12 weeks: results from BMS AI424-044, for the AI424-044 International Study Team, 6th International Conference on Drug Therapy in HIV Infection, Glasgow, UK, 17-21 November 2002.

Murphy R, Pokrovs.ky V, et al. Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or ATV: 108-week results of BMS study 008/044. Abstract 555, 10th CROI, Boston, February 2003.

O'Mara E, Randall D, Passarell J, et al., Population pharmacodynamic assessment of atazanavir exposure, uridine diphosphate-glucuronosyl transferase (UGT) 1A1 genotype and safety in healthy subjects, abstract A-1253, 42nd ICAAC, San Diego, 27-30 September 2002.

Piliero PJ. The utility of inhibitory quotients in determining the relative potency of protease inhibitors, AIDS 16(5); 2002.

Piscitelli S. Is lopinavir/ritonavir the most potent PI? http://www.medscape.com/medscape/HIV/AskExperts/2000/11/AIDS-ae105.html, 23 January 2001.

Prelutsky D, et al. Pharmacokinics of saquinavir hard gel (Invirase) when combined with atazanavir. 4th International Workshop in Clinical Pharmacology of HIV Therapy (IWCP) Cannes, 27-29 March 2003.

Rivero A, Delfraissy J-F, for the AI424-034 International Study Team, Atazanavir QD and Efavirenz QD With Fixed-Dose ZDV+3TC: Absence of Insulin Resistance Through Week 24 (AI424-034), 6th International Conference on Drug Therapy in HIV Infection, 17-21 November 2002, Glasgow, UK.

Squires KE, Thiry A, et al., for the AI424-034 International Study Team. Atazanavir (ATV) QD and efavirenz (EFV) QD with fixed-dose ZDV+3TC: comparison of antiviral efficacy and safety through wk 24 (AI424-034). Oral presentation H1076, 42nd ICAAC, San Diego, 27-30 September 2002.

Stevens RC, et al. Inhibitory quotient of protease inhibitors using a standardized determination of IC50. Abstract 4.2, 4th International Workshop on Clinical Pharmacology of HIV Therapy (IWCP), Cannes, 27-29 March 2003.

Taburet AM, Piketty C, Gérard L and the Puzzle 2 study group, abstr 537, Pharmacokinetic Parameters of Atazanavir/Ritonavir when Combined to Tenofovir in HIV Infected Patients with Multiple Treatment Failures: A Sub-study of Puzzle2-ANRS 107 trial. Abstract 537, 10th CROI, Boston, February 2003.

Tackett D, Child M, Agarwala S, et al. Atazanavir: a summary of two pharmacokinetic drug interaction studies in healthy subjects. Abstract 543, 10th CROI, Boston, February 2003.

U.S. Department of Health and Human Services, http://www.nih.gov, Technical note on atazanavir, the AIDSinfo Drugs Database.