

Objectives: Atazanavir (ATV) is a recently approved HIV protease inhibitor (PI). As with other PIs, careful attention to potential pharmacokinetic interactions in practice is necessary.

Design: The aim of this study was to assess trough plasma ATV concentrations in HIV positive individuals and to assess any associated factors.

Methods: Individuals established on an ATV containing regimen, completed an interviewer administered questionnaire recording ATV dosing characteristics, concomitant medication use and adherence. After completion, trough plasma ATV concentrations were measured.

Results: Of 100 individuals, mean trough plasma ATV concentrations ($\mu\text{g/L}$) were 282 (95%CI 95-468) and 774 (95%CI 646-902) in those on non- and ritonavir (RTV) boosted regimens respectively. 85 individuals had HIV RNA below detectable levels (<50 copies/mL). Seven individuals had ATV plasma levels below the assay limit of detection (<50 $\mu\text{g/L}$) all of whom had an undetectable plasma HIV RNA. In a multivariate analysis nevirapine use was associated with significantly lower trough ATV concentrations ($p=0.011$). Dosing characteristics including food taken, concomitant medications including drugs used for dyspepsia and HIV RNA were not significantly associated with trough ATV concentrations.

Conclusion: In this cohort, inherent variability was observed in trough plasma ATV concentrations but no significant association with dosing characteristics, concomitant medication or virological response observed. Further work is needed to assess the optimal dosing regimen when using ATV with nevirapine.

The Clinical Correlation's of Trough Plasma Atazanavir Concentrations in a Cohort of HIV-1-positive Individuals Receiving HAART

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Introduction

Atazanavir (ATV) is a new once-daily azapeptide inhibitor of HIV-1 protease. Nonlinear pharmacokinetics and clearance permit once daily dosing. Of importance it is the first protease inhibitor approved for once daily administration and has the lowest pill burden.

As with other protease inhibitors, careful attention to pharmacokinetic interactions with the use of ATV in clinical practice are necessary. With the widespread use of ATV, the aim of this study was to assess plasma trough concentrations of ATV from a cohort of HIV positive individuals receiving highly active antiretroviral therapy (HAART) containing ATV and to assess associations between ATV dosing and prescribing practices and observed trough plasma ATV concentrations.

Methods

Individuals established on ATV containing HAART for more than 28 days, attending for routine clinic visits between June 2004 and August 2004 were invited to participate. Participants completed an interviewer administered questionnaire and had a trough plasma ATV concentration assessed prior to their usual ATV dosing time.

Investigators documented all medications taken over a 24 hour period prior to the interview and specifically prompted every patient for the following categories of medication: antiretroviral therapy (ART), other prescribed medication, concomitant 'over the counter' medication, medications used for dyspepsia, supplementary medication, vitamins, mineral and herbal therapies, food supplements and recreational drugs.

Results

100 individuals completed the study; dosing regimens shown in Figure 1 and baseline characteristics in Table 1. Seven individuals had trough ATV concentrations below detectable limits (<50 $\mu\text{g/L}$) all of whom had undetectable plasma HIV RNA. In a multivariate analysis, the only antiretroviral agent significantly associated with lower trough ATV plasma concentrations was nevirapine (mean plasma ATV level 350 versus 726 $\mu\text{g/L}$, $p=0.011$). No dosing characteristic or concomitant medications were significantly associated with ATV plasma concentrations including drugs used for dyspepsia.

No significant associations were observed between individuals with detectable ($n=15$) and undetectable HIV RNA including ATV plasma concentration.

Figure 1: Dosing regimens of individuals completing study.

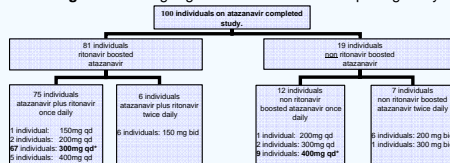


Table 1: Baseline and dosing characteristics	Value (number of patients unless otherwise stated)	Change in log ₁₀ atazanavir plasma level	95% CI for change	p value
Patient Characteristics				
Mean CD4 lymphocyte count, cells μL (range)	505 (48 – 1249)	-0.10	-0.23 to 0.03	0.129
Mean HIV RNA, copies/mL				
Number undetectable ($<=50$)	85			
Number detectable (>50)	15			
Mean viral load (range)	8 212 (50 – 635 000)	0.02	-0.11 to 0.15	0.787
Gender (male)	95	-0.42	-0.91 to 0.65	0.088
Mean time on atazanavir, range (days)	254, (43 – 612)	-0.02	-0.05 to 0.00	0.070
Dosing characteristics				
Trough atazanavir level, $\mu\text{g/L}$				
Mean non boosted atazanavir level (95% CI)	282 (95 – 468)			
Mean boosted atazanavir level (95% CI)	774 (646 – 902)			
With food	85	-0.05	-0.32 to 0.22	0.716*
With 20 g fat meal	49	0.05	-0.16 to 0.25	0.650*
pH Beverage, above 4	77	-0.11	-0.33 to 0.12	0.353*
Recommended dose	76	-0.03	-0.25 to 0.20	0.827*
Once daily versus twice daily dosing (number od)	87	0.08**	-0.21 to 0.37	0.574*
Missed dosage in past 3 days (no)	89	0.02	-0.11 to 0.15	0.748*
Adherence questionnaire result (above 95%)	79	0.05	-0.19 to 0.29	0.674*
Non-antiretroviral medication				
Any concomitant medication	91	0.34	-0.31 to 0.37	0.842
Concomitant medication with atazanavir***	37	0.11	-0.08 to 0.16	0.255
Angiotensin converting enzyme inhibitors	10	-0.01	-0.33 to 0.31	0.956
Anticoagulants	14	0.06	-0.19 to 0.37	0.533
Antivirals (others)	27	-0.01	-0.23 to 0.21	0.930
Benzodiazepines	19	0.06	-0.21 to 0.33	0.656
Cholesterol lowering agents	16	0.17	-0.10 to 0.43	0.203
Co-trimoxazole	11	0.07	-0.24 to 0.38	0.661
Drugs used for dyspepsia	12	0.02	-0.28 to 0.32	0.908
Nutritional supplements	10	0.06	-0.14 to 0.26	0.532
Non-steroidal anti-inflammatory agents	39	-0.03	-0.36 to 0.30	0.877
Other drugs (less than 5 individuals)	27	0.06	-0.15 to 0.28	0.568
* overall p value				
** overall results does not lie between stratified results because of an imbalance in relative frequencies. This is an example of Simpson's Paradox.				
*** concomitant medication = benzodiazepines, NSAID cox-2 inhibitors and drugs used for dyspepsia.				

Summary

In this cohort, inherent variability was observed in trough plasma ATV concentrations but no significant association with dosing characteristics, concomitant medication including drugs used for dyspepsia or virological response observed. Further work is needed to assess the optimal dosing regimen when using ATV with nevirapine.

Conclusion

In summary, in this cohort of individuals on ATV containing HAART regimens, trough plasma levels of ATV are significantly decreased with the use of nevirapine and not significantly altered by ATV dosing characteristics or the concomitant use of regularly prescribed and non-prescribed medication including drugs used for dyspepsia. Inherent variability is observed with ATV trough plasma levels as with the other PIs but is not associated with virological outcome. Further work is needed to assess the optimal dosage of ATV when prescribed with nevirapine; whether ATV/r-300/100 qd or a higher dose is optimal.

A recent report has described a 76% reduction in ATV AUC in healthy volunteers treated with ATV-r 300/100 qd and omeprazole 40mg. No significant changes in ATV exposure associated with drugs used for dyspepsia were observed in our cohort. Of those taking drugs used for dyspepsia, 10 of the 12 individuals took these agents at least 10 hours apart from ATV and both individuals receiving omeprazole reported taking a lower dose of 20 mg daily. These differences in dosing characteristics may not lead to a reduction in plasma ATV exposure.

These data do not support dose-modification of ATV based on plasma concentrations alone. Ongoing attention for potential interactions with the widespread use of ATV is warranted but from these data no unforeseen interactions are observed with commonly used medications or food/beverage restrictions in clinical practice.

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