

Tobacco and Marijuana Uses Significantly Decrease Atazanavir (ATV) Trough Concentrations in HIV Infected Individuals

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New York State Center of Excellence

in **Bioinformatics**
& Life Sciences



Abstract

Background: Atazanavir, a protease inhibitor, is a substrate and inhibitor of CYP3A. Substance related disorders (SRD) increase the risk of HIV transmission and may influence the progression and treatment of HIV infection. The objective was to evaluate the relationship between SRD and ATV trough concentrations along with immunologic and virologic responses.

Methods: 67 HIV positive individuals with (n=32) or without (n=35) SRD (defined per NIDA criteria for substance abuse) on ATV-containing antiretroviral treatment were enrolled and the association between substances such as alcohol, cocaine, heroin, marijuana, opioids and tobacco abuse to ATV trough concentrations, viral load and CD4 cell count was evaluated using Kruskal-Wallis and linear regression tests. Other demographics including race, gender, ethnicity and BMI were included in the analysis.

Results: The distribution of abused substances was 28%, 10%, 18%, 19%, and 49% for alcohol, cocaine, marijuana, opioids, and tobacco, respectively. 43% of these patients abused multiple substances. Significant reductions in ATV trough concentrations amongst tobacco and marijuana users were noted ($p < 0.05$). A large proportion of patients with SRD had concentrations below the therapeutic range (36% and 50% for tobacco and marijuana users, respectively, $p < 0.05$). SRD had no significant direct effects on viral response or CD4 count.

Conclusion: Tobacco and marijuana uses are associated with significantly low ATV trough concentrations. The cause of this association remains to be determined that could include enzyme induction. Further study of tobacco users is warranted as earlier pharmacokinetic studies may have reflected low daily smoking patterns compared to our patients.

Background

- Atazanavir (ATV) is the first-line protease inhibitor in the initial treatment of HIV infection. Despite the fixed daily dose of 300 mg ATV with 100 mg ritonavir in adults, it is characterized by significant interindividual pharmacokinetic variability resulting in variable response across patients.
- Previous studies have suggested a relationship between ATV drug exposure and antiviral response. However, long-term success in maintaining optimal therapeutic concentrations to sustain HIV suppression may be complicated by a variety of factors. These may include variable medication adherence, emergence of drug-resistant HIV, variable pharmacokinetics and substance related disorders.
- Individuals with substance related disorders (SRDs) are at higher risks for contracting and spreading HIV. Long-term antiretroviral efficacy becomes even more complex in HIV-infected individuals with SRDs due to additional factors including adherence barriers, co-morbidities, *e.g.* hepatitis B or C, depression, and complex drug-substance interactions.

Study Objectives

- To evaluate the relationship between substance related disorders and atazanavir pharmacokinetics, *i.e.* trough concentrations, along with immunologic and virologic responses.

Methods

- The study population (n=67) included patients who received atazanavir-containing therapy for > 6 months and were enrolled at 4 clinical sites including Bronx, NY; Rochester, NY; Miami, FL and Cleveland, OH between May 15, 2003 and May 15, 2007. The active substance abuse status was identified by clinicians at enrollment according to NIDA criteria.
- During the study period, patients were instructed to complete three clinic visits, entry, trough and directly observed therapy (DOT), and take scheduled doses of atazanavir at the same time for 4 days before each visit. Plasma samples were collected for drug assay and pharmacokinetic evaluation.
- Adherence assessment and counseling prior to plasma sampling and each scheduled clinic visit were performed and recorded. Laboratory data *e.g.* CD4+ cell counts and HIV RNA were recorded during the clinic visits.
- Plasma atazanavir concentrations were measured using a HPLC method previously developed, validated, and certified by the New York State Department of Health at Core Analytical Laboratory, University at Buffalo.
- **Statistical analysis:**
 - Continuous variables were compared by the Kruskal-Wallis test, and categorical variables were compared by the chi-square and Fisher's exact tests.
 - Multiple linear regression models were used to determine factors associated with atazanavir concentrations, immunological and virologic responses while adjusting for covariates.

Results

- The distribution of abused substances was 41%, 19%, 38%, 22%, and 91% for alcohol, cocaine, marijuana, opioids, and tobacco, respectively, among substance abusers. 43% of these patients abused multiple substances.
- Significant reductions in ATV trough concentrations amongst tobacco and marijuana users were noted ($p < 0.05$), but not with alcohol, cocaine or therapeutic opioid users (**Table 1, Figures 1 and 2**).
- A large proportion of patients with SRD had concentrations below the therapeutic range (36% and 50% for tobacco and marijuana users, respectively, $p < 0.05$) (**Figures 3 and 4**).
- SRD had no significant direct effects on viral response or CD4 count (**Table 2**).

Results

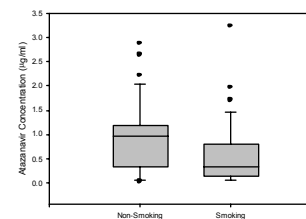


Figure 1. Effect of smoking on atazanavir trough concentrations

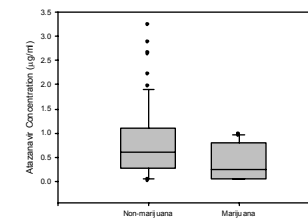


Figure 2. Effect of marijuana use on atazanavir trough concentrations

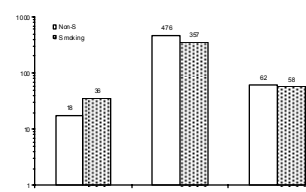


Figure 3. Effect of smoking on atazanavir trough concentrations, CD4 counts and viral load

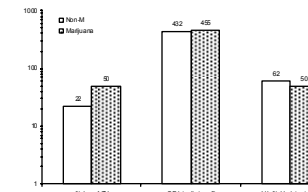


Figure 4. Effect of marijuana use on atazanavir concentrations, CD4 counts and viral load

Table 1. Influence of substance related disorders (SRD) on atazanavir trough concentrations – median, µg/ml (IQR)

	SRD	Non-SRD	P
Tobacco	0.314 (0.121-0.790)	0.957 (0.325-1.196)	0.009
Marijuana	0.238 (0.050-0.801)	0.593 (0.272-1.111)	0.030
Alcohol	0.534 (0.134-0.913)	0.558 (0.218-1.085)	0.597
Cocaine	0.768 (0.050-1.393)	0.544 (0.192-1.051)	0.920
Opioids	0.325 (0.149-0.773)	0.712 (0.194-1.098)	0.220

Table 2. Substance related disorders (SRD) had no significant direct effects on viral load or CD4 counts in HIV+ patients receiving atazanavir

Characteristics (Mean ± SD)	SRD	Non-SRD	P
No. of subjects	32	35	--
Males (%)	43 (64)	19 (59)	24 (69)
Age, years	46 ± 8	45 ± 6	46 ± 10
CD4 counts, cells/mm ³	454 ± 296	462 ± 344	446 ± 246
HIV-1 viral load, log ₁₀ copies/ml	4.4 ± 5.0	4.4 ± 4.9	4.4 ± 5.1
Presence of HCV antibodies, %	25	28	23

Conclusions

- Tobacco and marijuana use is inversely related to atazanavir trough concentrations.
- Although substance related disorders had no significant direct effects on treatment outcomes, the relatively low CD4 counts and high viral loads among patients with tobacco and marijuana use suggest drug-substance interactions might contribute to inter-individual variability in patients' response to atazanavir-containing regimen.
- The underlying mechanism for these observations may include metabolizing enzyme induction that warrants further investigation.
- Clinicians should consider these pharmacologic findings when developing ART regimens for HIV+ patients with substance related disorders.

Acknowledgment

The contributions of Raju Sada, Julie Sarlo, Carol Greisberger, Leslie Thompson, Norma Storer and the clinical research staff at the Montefiore Medical Center AIDS Center, the University of Rochester HIV Program, the University of Miami AIDS Research Unit, and the University Hospitals, Case Medical Center HIV Program and the patients at each of the participating HIV treatment centers is appreciated. The dedication of the research staff and students from the UB Core Analytical Laboratory is also appreciated. This research was supported by grant IR01DA-015024 from the National Institute on Drug Abuse. Dr. Zingman is supported in part by the Center for AIDS Research at the Albert Einstein College of Medicine and Montefiore Medical Center (IR01AI-51519). Dr Fehintola is supported in part by the AIDS International Training and Research Program at Northwestern University (1D43TW007995-01A1).