Therapeutic Monitoring and Variability of Atazanavir in HIV-Infected Patients, With and Without HCV Coinfection, Receiving Boosted or Unboosted Regimens

Mario Regazzi, PharmD, Paola Villani, BiolD,* Roberto Gulminetti, MD,† Maria Cusato, PharmD,* Michela Brandolini, MD,† Carmine Tinelli, MD,‡ Alessandra Barassi, MD,§ Renato Maserati, MD,† Laura Sighinolfi, MD,¶ Antonella D'Arminio Monforte, MD,§ and Gian Vico Melzi D'Eril, MD§*

Background: Adequate plasma trough concentrations (C_{trough}) of protease inhibitors are required to maintain antiviral activity throughout the dosing interval. Therapeutic drug monitoring is used in clinical practice to optimize dosage and avoid toxic or subtherapeutic drug exposure. The pharmacokinetic variability of Atazanavir (ATV) can be relatively large, as a result of several factors. One of the affecting factors may be hepatic impairment due to hepatitis C virus (HCV) coinfection.

Methods: We collected trough plasma samples from human immunodeficiency virus (HIV)-1–infected outpatients, with and without HCV coinfection and/or cirrhosis, receiving stable highly active antiretroviral therapy containing ATV. In the total population, we mainly compared the 2 regimens: 300ATV + 100RTV OD [ritonavir (RTV), once daily (OD)] versus 400ATV OD. We used a threshold value of 0.15 μg/mL, based on the proposed therapeutic range (0.15–0.85 μg/mL). Plasma concentrations of ATV were determined by a validated assay using high-performance liquid chromatography with ultraviolet detection. A total of 214 HIV-infected outpatients were included. For each regimen, we compared 3 groups of subjects: HIV+/HCV−, HIV+/HCV+, and HIV+/HCV+ with cirrhosis.

Results: In the whole study population, we observed a large variability and found suboptimal C_{trough} levels (<0.15 μg/mL) in 23 subjects (2 belonging to the 300/100 OD group and 21 to the 400 OD group). For the standard dosage regimen of 300ATV + 100RTV OD, we did not find a statistical difference between HIV-infected patients without HCV coinfection versus HIV-infected patients with HCV coinfection: median 0.85 (interquartile range 0.53–1.34) and 0.95 (0.70–1.36) μg/mL, respectively. In HIV+/HCV+-infected patients with cirrhosis, we found a median C_{trough} of 0.70 (0.43–1.0) μg/mL, with no statistical difference when compared with HIV+/HCV− infected patients. For the 400ATV OD (n = 90) dosage regimen, the total median ATV C_{trough} was 0.40 (0.23–1.0) μg/mL. In this group, we found a statistically significant difference between HIV+/HCV− and HIV+/HCV+-infected patients: median C_{trough} was 0.23 (0.11–0.42) and 0.52 (0.20–1.0) μg/mL, respectively. In HIV+/HCV+ subjects with cirrhosis, the C_{trough} median value was 0.42 (0.13–0.75) μg/mL, and there was a significant difference when compared with HIV patients without coinfection.

Conclusions: Therapeutic drug monitoring of ATV in patients receiving unboosted regimen may be useful to identify those HIV-infected subjects, with or without HCV coinfection, who may benefit from adding low RTV doses, or the subset of patients in whom removal of RTV could be attempted without the risk of suboptimal plasma ATV exposure.

Key Words: HIV, HCV coinfection, atazanavir, therapeutic drug monitoring

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INTRODUCTION

The management of human immunodeficiency virus (HIV) infection is complex, because there is great interpatient variability in the absorption, distribution and elimination of antiretroviral agents. Therefore, therapeutic drug monitoring (TDM) has been proposed as a useful strategy to individualize therapy for people with HIV.[1–4]

Protease inhibitors (PIs) are one of the main classes of antiretroviral drugs recommended for the initial treatment of HIV-1–infected patients and are often boosted with ritonavir (RTV), which increases systemic exposure, reduces the risk of resistance, and decreases the administration frequency.[5]

Atazanavir (ATV) is a potent azapeptide PI, administrated in combination with other antiretrovirals for HIV-1 treatment. Interpatient variability in ATV pharmacokinetics is relatively large and may be a result of several factors. One potential contributing mechanism is hepatic impairment due to hepatitis C virus (HCV) or hepatitis B virus (HBV) coinfection, which occurs in approximately 30% of HIV-infected individuals in the United States and up to 50% in Mediterranean countries.[6,7] Liver impairment caused by hepatitis infections may impact the absorption of the drug

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From the *Clinical Pharmacokinetics Laboratory; †Infectious Diseases Department; ‡Clinical Epidemiology and Biometric Unit, Foundation IRCCS S. Matteo Hospital, Pavia; §Department of Medicine, Surgery and Dentistry, University of Milano, San Paolo Hospital, Milano; and ¶Infectious Diseases Department, S. Anna Hospital, Ferrara, Italy.

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Correspondence: Mario Regazzi, PharmD, Clinical Pharmacokinetics Laboratory, Foundation IRCCS San Matteo, Hospital, Piazzale Golgi 2 27100 Pavia, Italy (e-mail: regazzim@smatteo.pv.it).

and its metabolism, as ATV is extensively metabolized in the liver, principally by CYP3A4/3A5 hepatic enzymes.

As with other PIs, quantifying and explaining the variability in ATV exposure by means of TDM are crucial for better pharmacotherapy management. It has been recently reported for ATV that both virologic efficacy and toxicity seem to be concentration dependent. ATV trough concentrations ranging from 0.15 to 0.85 μg/mL have been shown to give the highest probability of virologic response and the lowest probability of side effects.[8,9]

The objective of this study was to analyze TDM data obtained during ATV treatment of HIV-infected patients with and without hepatitis coinfection, receiving boosted or unboosted regimens, with particular attention to the difference between the 2 regimens and the potential influence of hepatic impairment on ATV plasma concentrations.

MATERIALS AND METHODS

Study Population

We performed a multicenter, retrospective, observational study. We evaluated plasma samples from a cohort of 214 HIV-1–infected outpatients, with and without HCV/HBV coinfection and/or cirrhosis, at 3 different Clinical Centers, within the context of a routine TDM program. All patients were receiving RTV-boosted or unboosted ATV as part of their antiretroviral therapy (ART). In addition to dosing- and sampling-time information, the following data were recorded for each patient: sex, body weight, age, race, CD4 T-cell count, viral load, transaminase and bilirubin levels, HCV/HBV coinfection, and concomitant medications.

The patients were stratified as (1) HIV-infected patients non-coinfected; (2) HIV-infected patients with chronic hepatitis (documented by detectable plasma HCV-RNA or HBV-DNA) without cirrhosis; and (3) HIV-infected patients with HCV/HBV-related liver cirrhosis.

The diagnosis of cirrhosis was made by assessing the AST Platelet Ratio Index (APRI) score, a simple test that employs the aspartate aminotransferase (AST) to platelet ratio as an indirect marker of hepatic fibrosis. The APRI-positive predictive value is ≥ 1.5, and the negative predictive value, for excluding significant fibrosis is <0.5.[10]

Pharmacokinetic Sampling and Analytical Method

Pharmacokinetic assays were centralized at the Laboratory of Clinical Pharmacokinetics, Foundation IRCCS San Matteo Hospital, Pavia, Italy.

ATV plasma concentrations were obtained in the context of routine drug monitoring and according to the procedures established at our Institutions. Ethics Committee approval was not required for studies using routine monitoring data.

To determine C_{trough}, blood samples were drawn in the morning, under steady-state conditions (ie, the drug regimen was unchanged for at least 1 month), just before therapy administration. The window for blood sample collection was 22–26 hours. The time of the last ATV dose was ascertained by patient report. No other specific measure of adherence was used. Blood samples (5 mL) were collected into lithium heparin or potassium-ethylenediaminetetraacetic acid Monovette syringes (Sarstedt, Numbrecht, Germany). Plasma was separated by centrifugation and virus inactivated in a water bath at 56°C for 45 minutes, and stored at −20°C until analysis. ATV plasma concentrations were determined by a validated modified method using high-performance liquid chromatography with ultraviolet detection. [11] Briefly, after liquid-liquid extraction in 3 mL of ethyl acetate–hexane, the samples were separated via reverse-phase liquid chromatography on a Hypersil BDS C18 (4.6 × 250 mm, 5 μm) analytical column under isocratic conditions (60% H_3PO_4 0.1% in H_2O, pH 7.2: 40% acetonitrile). UV detection at 220 nm provides adequate sensitivity with minimal interference from endogenous matrix components. The calibration curve was linear over a concentration range of 0.05–10 μg/mL with a 0.05-μg/mL limit of quantification and a lower limit of detection of 0.02 μg/mL. The method is specific, accurate, and precise. Intraassay coefficients of variation for ATV quality control concentrations were 8.6%, 9.5%, and 9.7% for the low, medium, and high quality control, respectively. Interassay coefficients of variation were 7.8%, 8.9%, and 9.1%, respectively. The corresponding accuracy ranged between 95% and 103%. Our laboratory is included in an external quality assurance program (Association for Quality Assessment in TDM and Clinical Toxicology, The Netherlands).

The proportion of patients with an ATV C_{trough} below the suggested target value of 0.15 μg/mL was estimated. We used the threshold value of 0.15 μg/mL, based on the previously proposed therapeutic range (0.15–0.85 μg/mL).[12,13] Therefore, an ATV C_{trough} below this value was defined as 'suboptimal.' We also compared data obtained from the 2 ATV regimens among the different HIV-infected subject populations, in relation to the presence of hepatitis coinfection and/or cirrhosis.

Statistical Analyses

Median, lnterquartile range (IQR), and 5°–95° percentiles were used to summarize quantitative variables that were not normally distributed (Shapiro test). Count and percentage were used for qualitative variables. Differences between >2 groups were evaluated with the Mann–Whitney test, whereas differences between >2 patient groups were assessed by the Kruskall–Wallis test. Corrections for multiple comparisons were not performed for pairwise comparison, as the study was intended as exploratory, not explicative. The Chi-square (χ^2) test or Fisher exact test was used for qualitative variables. A P value of <0.05 was considered statistically significant, and all tests were 2 sided. Data analysis was performed with the STATA statistical package (Ver. 10.0, 2009, Stata Corporation, College Station, TX).

RESULTS

A total of 214 HIV-infected outpatients (148 men and 66 women) receiving antiretroviral regimens containing ATV, were evaluated for ATV C_{trough} levels. Patients received boosted or unboosted ATV once daily, associated with 2 nucleoside reverse transcriptase inhibitors. The most common regimens prescribed, including 2 nucleoside reverse

transcriptase inhibitors, were lamivudine plus abacavir, tenofovir plus emtricitabine, tenofovir plus lamivudine, lamivudine plus zidovudine, or tenofovir plus didanosine (didanosine was administered 2 hours after ATV or in an enteric-coated formulation, to avoid interaction of the antacid with ATV). No drug known to interact with ATV therapy was coadministered.[12,13]

The percentage of patients with an HIV-1 RNA load <50 copies per milliliter was similar between patients receiving boosted or unboosted ATV. Overall, the patients receiving boosted or unboosted ATV therapy were comparable regarding demographic and clinical characteristics and concomitant ART. The patients were divided into 3 groups: HIV+ without coinfection, HIV+/HCV+ and HIV+HCV+ with cirrhosis. Patients' demographic and clinical characteristics are reported in Tables1 and 2 (expressed as median, IQR, and 5°–95° percentiles).

We first evaluated the 2 regimens: 300ATV + 100RTV OD versus 400ATV OD. The first regimen (300/100 OD) included 124 patients: 73 HIV+/HCV–, 26 HCV+/HCV+, and 25 HIV+/HCV+ with cirrhosis. For the standard dosage of 300ATV + 100RTV OD, the total median ATV C_{trough} was 0.90 (IQR 0.43–1.36) μg/mL. We observed a large variability and found suboptimal C_{trough} levels (<0.15 μg/mL) in 2 subjects only, who had no measurable viral load.

The second regimen (400 OD) included 90 subjects: 38 HIV+/HCV–, 28 HIV+/HCV+, and 24 HIV+/HCV+ with cirrhosis. For the 400ATV OD dosage, the total median ATV C_{trough} was 0.40 (0.23–1.0) μg/mL. We observed a large variability and found suboptimal C_{trough} levels in 21 subjects (4 patients had measurable viral load, ranging from 677 to 17,180 copies per milliliter).

For each regimen, we compared 3 groups of subjects: HIV+/HCV−, HIV+/HCV+, HIV+/HCV+ with cirrhosis (Table 3). In the first regimen (300/100 OD), we did not find a statistical difference between HIV+ patients without HCV coinfection versus HIV+ patients with HCV coinfection: median 0.85 (IQR 0.53–1.34) and 0.96 (0.70–1.36) μg/mL, respectively. In cirrhotic patients, we found a median C_{trough} of 0.70 (0.43–1.0) μ/mL with no statistical difference when compared with HIV+/HCV− and with HIV+/HCV+ patients.

In the second regimen group (400 OD), we found a statistically significant difference between HIV+/HCV− and HIV+/HCV+ patients: median C_{trough} was 0.23 (IQR 0.11–0.42) and 0.52 (0.20–1.0) μg/mL, respectively ($P = 0.005$). In cirrhotic subjects, the C_{trough} median value was 0.42 (0.13–0.75) μg/mL, and there was a significant difference when compared with HIV+ patients without coinfection ($P = 0.044$).

The 400 mg OD unboosted regimen in HIV+/HCV– subjects provided significantly lower ATV trough concentrations than did the standard dosage of 300ATV+100RTV OD (median 0.23 versus 0.85 μg/mL; $P < 0.0001$). The same difference between the 2 ATV regimens was also confirmed in HIV+/HCV+ patients (0.52 μg/mL for the 400 OD and 0.96 μg/mL for the 300/100 OD, respectively).

Cirrhotic patients had a slightly lower C_{trough} median value in the 300/100 OD regimen (0.70 μg/mL) but a higher median value in the 400 OD regimen (0.42 μ/mL), when compared with the HIV+/HCV− patient groups (0.85 and 0.23 μg/mL, respectively).

DISCUSSION

We report the results of an observational study using TDM as a surveillance tool to monitor ATV therapy in the clinical setting. ATV is approved in Europe and in the United States at a dose of 300 mg boosted with 100 mg of RTV once daily (ATV/RTV 300/100 mg OD) to be taken with food, but it is also approved unboosted at 400 mg once daily for treatment-*naive* patients.[12,13] In patients with hepatic impairment, ATV should be used with caution in the case of mild to moderate dysfunction (Child–Pugh category A) and the oral ATV dose needs to be adjusted in moderate impairment (Child–Pugh category B), with a reduction to 300 mg daily. For severe hepatic impairment (Child–Pugh category C), ATV is not recommended. RTV-boosted ATV regimens should be used with caution in patients with mild hepatic impairment and should not be used in those with moderate to severe hepatic impairment.[12,13] The dosage precautions for the use of ATV in these clinical situations are based on limited available pharmacokinetic and safety data in subjects with hepatic impairment, for both regimens.

The results of our pharmacokinetic study, obtained from the comparison of the 2 regimens, confirm the large interindividual variability in ATV C_{trough}, particularly with the 400 OD regimen. The data also illustrate how ATV trough levels in plasma may be lower than the proposed target concentration, particularly when it is not boosted with low-dose RTV. This observation is in accordance with the results of Stohr et al,[14] who found that there is a high probability of an ATV trough concentration below the recommended therapeutic range with the unboosted 400-mg regimen. Also, in keeping with the findings of Flexner,[15] we observed that the high variability in the ATV plasma concentrations may be reduced, but not eliminated, with RTV boosting. High ATV interindividual variability has also been demonstrated in several previous studies.[2,16,17]

Our results are similar to those of Winston et al who evaluated ATV C_{trough} concentrations in a cohort of patients with HIV-1 (n = 100) and found a mean ATV value of 0.28 (95% confidence interval 0.095–0.47) μg/mL (n = 19) in nonboosted regimens and a mean ATV value of 0.77 (95% confidence interval 0.65–0.90) μg/mL (n = 81) in RTV-boosted regimens.[18] Another study by Agarwala et al[19] reported a mean of 0.27 and 0.86 μg/mL for nonboosted and boosted regimens, respectively.

ATV is extensively metabolized in the liver, principally by CYP3A4/3A5 enzymes, and hepatic impairment may contribute to ATV variability. Thus, it is difficult to predict the impact of liver disease on the metabolism and pharmacokinetics and to provide general dosing guidelines for these subjects.[20,21] The situation is further complicated by the presence or the absence of the RTV booster effect, and the results are controversial.

Data on the incidence of liver toxicity due to ATV/RTV, in the specific subset of HIV/hepatitis coinfected individuals, are very limited and come from relatively small populations.[14,22] Available data recommend avoiding

TABLE 1. Characteristics of the Study Population Receiving ATV 300/100rtv OD Regimen, Median (IQR)

Characteristics	HIV (n = 73)	HIV/HCV (n = 26)	HIV/HCV Cirrhosis (n = 25)
Sex M/F	47/26	19/7	21/4
Age (yrs)	45 (41–50)	45 (42–46)	47 (41–48)
Weight (kg)	68 (56–73)	65 (53–78)	77 (55–85)
$CD4^+$ (cells per cubic millimeter)	501 (335–666)	463 (382–661)	512 (357–665)
Plasma HIV load <50 copies per milliliter (%)	91	92	96
ALT (IU/L)	24 (17–32)	31 (20–44)	60 (37–107)
AST (IU/L)	24 (19–29)	33 (23–52)	55 (32–80)
Albumin (g/dL)	4.25 (4.16–4.43)	4.28 (4.17–4.5)	4.14 (4.12–4.18)
Total bilirubin (mg/dL)	2.62 (1.48–3.88)	2.84 (2.32–4.78)	2.87 (2.08–3.94)
Plt (cells per cubic millimeter)	219,500 (186,500–262,000)	228,000 (216,000–258,000)	138,000 (125,000–165,000)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Plt, platelet count.

ATV/RTV in patients with cirrhosis and moderate to severe hepatic insufficiency although Barreiro et al[23] suggest that this recommendation should be reconsidered. Our data are in agreement with those of other studies reporting that hepatic impairment does alter the pharmacokinetics of ATV.[13,24]

In our patients, the 400 mg OD unboosted regimen in HIV+/HCV-negative subjects provided significantly lower ATV trough concentrations than did the standard dosage of 300ATV + 100RTV OD (median 0.23 versus 0.85 μg/mL; $P < 0.0001$). The same difference between the 2 ATV regimens was also confirmed in HIV+/HCV-positive patients (0.52 μg/mL for the 400 OD and 0.96 μg/mL for the 300/100 OD, respectively). Cirrhotic patients had a slightly lower C_{trough} median value in the 300/100 OD regimen (0.70 μg/mL) but a higher median value in the 400 OD regimen (0.42 μg/mL) when compared with HIV+/HCV-negative patient groups (0.85 and 0.23 μg/mL, respectively). It should be underscored that even considering the elevated levels in cirrhotic and HCV-negative patients, the concentrations obtained with the 400-mg unboosted regimen were lower than the corresponding concentrations obtained with the 300/100 boosted regimen.

In the unboosted 400-mg regimen (Table 3), there was a statistically significant difference between HIV patients with normal hepatic function and HIV+/HCV+-infected patients with or without cirrhosis. In this group of coinfected subjects, hepatic dysfunction may lead to significantly higher ATV plasma levels, when compared with normal HIV-infected subjects.

In our study, in contrast to the data obtained in the ATV 400-mg unboosted regimen, in the 300/100 regimen, the 3 groups of patients (HIV+/HCV−, HIV+/HCV+, and HIV+/HCV+ with cirrhosis) had similar trough concentrations. The absence of a statistical difference in trough plasma concentrations among the 3 groups of patients on the boosted regimen 300/100 may be explained by the presence of RTV, which inhibits hepatic metabolism, and thus the expected reduction in clearance for patients with hepatic dysfunction may be absent or less pronounced. Results from other studies support the concept that the intrinsic clearance of PIs in patients with liver disease is only partially affected after being inhibited by low-dose RTV coadministration, because no significant changes in drug pharmacokinetics in mild liver dysfunction with morphologic evidence of cirrhosis were observed.[23–27]

This PK study has some limitations. First of all, it was based on a retrospective observational TDM data set and not on a controlled protocol. Also, the potentially confounding impact of other drug therapy, such as coadministration of tenofovir [tenofovir disoproxil fumarate (TDF)] was not addressed in our analysis, as the presence of this nucleotide analog reverse transcriptase inhibitor in the concomitant therapy was equally distributed among all patient groups;

TABLE 2. Characteristics of the Study Population Receiving ATV 400 OD Regimen, Median (IQR)

Characteristic	HIV (n = 38)	HIV/HCV (n = 28)	HIV/HCV Cirrhosis (n = 24)
Sex M/F	21/17	23/5	17/7
Age (yrs)	41 (38–48)	45 (42–48)	45 (41–53)
Weight (kg)	65 (53–78)	73 (60–78)	65 (57–78)
$CD4^+$ (cells per cubic millimeter)	574 (466–688)	626 (432–811)	488 (333–656)
Plasma HIV load <50 copies per milliliter (%)	81	89	83
ALT (IU/L)	27 (17–48)	51 (23–73)	71 (49–88)
AST (IU/L)	21 (17–29)	42 (26–51)	59 (41–80)
Albumin (g/dL)	4.1 (4.13–4.45)	4.0 (3.9–4.4)	3.8 (2.5–3.9)
Total bilirubin (mg/dL)	1.59 (0.9–2.68)	2.2 (1.1–3.5)	1.8 (1.32–2.42)
Plt (cells per cubic millimeter)	232,000 (210,000–265,000)	235,500(148,000–286,000)	135,000 (112,500–165,000)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; Plt, platelet count.

TABLE 3. ATV Plasma Levels (C_{trough}, μg/mL) in the 3 Patient Groups According to the 2 Dosage Regimens Expressed as Median, IQR and 5°–95° Percentiles

ATV Dose (mg)	Group 1: HIV+	Group 2: HIV+/HCV+	Group 3: HIV+/HCV+ with cirrhosis
300/100rtv OD	*n* = 73	*n* = 26	*n* = 25
Median	0.85	0.96	0.70
IQR	0.53–1.34	0.70–1.36	0.43–1.0
5°–95° percentile	0.19–2.70	0.46–1.97	0.23–2.09
400 OD	*n* = 38	*n* = 28	*n* = 24
Median	0.23*†	0.52*	0.42†
IQR	0.11–0.42	(0.2–1.0)	0.13–0.75
5°–95° Percentile	<0.05–2.10	<0.05–4.40	<0.05–1.95
Comparison of dosage regimens (*P* value)	*P* = 0.0001	*P* = 0.00308	*P* = 0.021231

*Group 1 versus group 2, *P* = 0.00467.
†Group 1 versus group 3, *P* = 0.04421.

notably, the proportion of HIV patients with and without coinfection treated with TDF was essentially similar (61% versus 49%, respectively). In addition, the literature data report conflicting results on the effect of TDF on ATV exposure: In some studies, ATV exposure was decreased by TDF, in both boosted and unboosted regimens[28,29], but in other observational studies, no influence was found.[14,30]

However, the results of this observational study should contribute to ATV therapy monitoring, as they reflect real-life clinical settings in a particular population, HIV/HCV-coinfected patients, with or without cirrhosis, in which there are limited and contrasting PK data.

When we analyzed the plasma concentrations of the 2 therapy regimens in relationship to the reference target concentration (0.15 μg/mL), in the nonboosted regimen, the percentage of patients with a plasma level (C_{trough}) below the target concentration was elevated (26%) with respect to the 2% observed in the boosted regimen. However, in HIV+/HCV+-infected patients receiving unboosted regimen, only 14% had suboptimal plasma levels. Our data confirm that TDM offers useful additional information in support of ATV individualized dose adjustment.

From a pharmacokinetic point of view, HIV subjects, with or without HCV coinfection and/or cirrhosis (mild–moderate), will have increased exposure when adding low-dose RTV, but in a subset of patients, the removal of RTV could be attempted without risking suboptimal plasma ATV exposure and subsequent virological failure. At present, only TDM can differentiate between these 2 very distinct situations.

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