Pharmacokinetic-pharmacodynamic modeling of unboosted atazanavir in a cohort of stable HIV-infected patients

Sylvain Goutelle, Thomas Baudry, Marie-Claude Gagnieu, André Boibieux, Jean-Michel Livrozet, Dominique Peyramond, Christian Chidiac, Michel Tod, Tristan Ferry, on behalf of the Lyon HIV Cohort Study Group

1 Service Pharmaceutique – Groupement Hospitalier de Gériatrie, 2 Service de Maladies Infectieuses et Tropicale, 3 Laboratoire de Biochimie et Biologie Moléculaire - UF de Pharmacologie Spécialisée, Groupement Hospitalier E. Herriot, 4 Service Pharmaceutique, Groupement Hospitalier Nord, and 5 Service d’Immunologie Clinique, Hospices Civils de Lyon, Lyon, France

6 Université Claude Bernard Lyon 1, Lyon, France
7 Laboratoire de Biométrie et Biologie Evolutive, UMR CNRS 5558, Villeurbanne, France
8 INSERM U851, Immunité, Infection, Vaccination, Lyon, France

‡ Sylvain Goutelle and Thomas Baudry contributed equally to the work

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# Corresponding authors

Professor Christian Chidiac, Service de Maladies Infectieuses et Tropicales, Hôpital de la Croix-Rousse, Hospices Civils de Lyon

103 Grande Rue de la Croix-Rousse, 69004, Lyon, France

Phone: +33 (0)4 72 07 11 07

Fax: +33 (0)4 72 07 17 50

E-mail: christian.chidiac@chu-lyon.fr

Sylvain Goutelle, Service Pharmaceutique, Hôpital Pierre Garraud, 136 rue du Commandant Charcot, 69005, Lyon, France

Phone: +33 (0)4 72 16 80 99

Fax: +33 (0)4 72 16 81 02

E-mail: sylvain.goutelle@chu-lyon.fr
Abstract

Limited data are available on the pharmacokinetics and pharmacodynamics (PK/PD) of unboosted atazanavir (uATV) in treatment-experienced patients. The aim of this work was to study the PK/PD of unboosted atazanavir in a cohort of HIV-infected patients. Data were available for 58 HIV-infected patients (69 uATV-based regimens). Atazanavir concentrations were analyzed by using population approach and the relationship between atazanavir PK and clinical outcome was examined using logistic regression.

The final PK model was a linear one-compartment model with a mixture absorption model to account for two subgroups of absorbers. The mean (interindividual variability) of population PK parameters were: clearance, 13.4 L/h (40.7%), volume of distribution, 71.1 L (29.7%), and fraction of regular absorbers, 0.49. Seven subjects experienced virological failure after switch to uATV. All of them were identified as low absorbers in the PK modeling. The absorption rate constant (0.38 ± 0.20 versus 0.75 ± 0.28 h⁻¹, \( p = 0.002 \)) and ATV exposure (AUC₀⁻²₄, 10.3 ± 2.1 versus 22.4 ± 11.2 mg.h.L⁻¹, \( p = 0.001 \)) were significantly lower in patients with virological failure than in patients without failure. In the logistic regression analysis, both the absorption rate constant and ATV trough concentration significantly influenced the probability of virological failure.

Significant relationship between ATV pharmacokinetics and virological response has been observed in a cohort of HIV-patients who were administered unboosted atazanavir. This study also suggests that twice daily administration of uATV may optimize drug therapy.
Introduction

Current international guidelines for the antiretroviral treatment of adult human immunodeficiency virus (HIV) infection recommend a combined initial regimen usually based on three antiretroviral drugs (1). The association of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a ritonavir-boosted protease inhibitor (PI) is one of the first-line options, and atazanavir (ATV) is one of the two recommended PI in such a regimen.

Atazanavir with ritonavir boosting is the only PI for which non-inferiority to efavirenz-based regimens has been demonstrated in a randomized trial (1, 2). The recommended dose of ATV in adults is 300 mg, with 100 mg of ritonavir, once daily.

However, poor tolerance and drug-drug interactions, due to ritonavir in part, may complicate ritonavir-boosted atazanavir therapy in some patients. Unboosted atazanavir (uATV) may be an attractive option to face those issues (3). It has been shown that uATV-based therapy was non-inferior to ritonavir-boosted therapy in adult treatment-naïve patients in controlling HIV infection after an initial induction treatment with ritonavir-boosted ATV (4, 5). Compared with ritonavir-boosted therapy, unboosted ATV therapy is associated with significantly lower ATV trough concentrations as well as overall exposure (6, 7). Unboosted ATV has been approved by the FDA, as a 400 mg once daily regimen, and atazanavir is currently the only PI that may be administered unboosted.

Although unboosted atazanavir is not approved by the European Medicines Agency, large cohort studies have indicated that a significant proportion of patients do receive unboosted ATV in Europe (8-10), notably as a simplification strategy in treatment experienced HIV-infected patients. Those cohort studies have confirmed that, in patients with stable virological suppression and no prior history of virological failure, switch to unboosted atazanavir has a good efficacy and safety profile.
Early phase II data from ATV manufacturer have demonstrated a relationship between ATV exposure and both efficacy (log drop in viral load) and safety (hyperbilirubinemia) (11). However, the “real-life” cohort studies above cited did not explore relationships between ATV exposure and outcome. Actually, limited data are available on the pharmacokinetics and pharmacodynamics (PK/PD) of unboosted atazanavir in treatment-experienced HIV-infected patients. The objective of this study was to perform PK/PD modeling of atazanavir in a cohort of stable HIV-infected patients who were administered uATV.
Methods

Study design, patient population and data collection

This was a retrospective data analysis from a prospective observational cohort of HIV-infected patients followed in the Lyon area (France) called “Lyon HIV cohort study” (3,200 patients are currently followed). All data used in this study were collected during routine patients’ care between 2004 and 2009. Inclusion criteria for the analysis were as follows: 1/ patients with undetectable viral load before introduction of uATV, 2/ patients who were administered uATV for at least one month, whatever the backbone was, 3/ patients with at least one ATV plasma concentration measured at the steady state. Patients who were administered uATV under the same dosage regimen for at least two weeks, either once daily or twice daily, were considered to be at the steady state. All individuals from the cohort who met the inclusion criteria were included in the analysis. Subjects who were administered more than one uATV-based regimen, because of change in companion anti-HIV drugs or ATV dose for example, were included as independent individuals.

Information on atazanavir dosage regimens, blood sampling times, and ATV plasma concentrations was retrieved from the patients’ electronic and manuscript medical files.

Demographic data collected and tested in the model building included age, sex, and total body weight. Glomerular filtration rate (GFR) was estimated by the abbreviated Modification of Diet in Renal Disease (MDRD) equation (12). Renal function was also tested as a categorical variable in the covariate model building. Patients with estimated GFR ≤ 60 ml/min were considered as having impaired renal function. All medications that were co-administered to patients under uATV, including the other antiretroviral drugs were recorded. Documented drug-drug interactions (DDI) were identified and classified in two groups in the covariate analysis: DDI that may decrease ATV exposure (e.g., tenofovir, proton-pump inhibitors, H2-
receptor antagonists) and DDI that may increase ATV exposure (e.g. triazole antifungal agents). The dosage frequency was also examined as a covariate in both pharmacokinetic and pharmacodynamic model buildings.

Virological outcome was monitored after switch to uATV. Virological failure was defined as two consecutive HIV viral load > 40 copies/ml in patients with undetectable viral load before switch to uATV.

Atazanavir assay

Atazanavir plasma concentrations were measured by a validated reverse-phase HPLC method using an UV-diode array detector. Concentrations were determined at three wavelengths (216, 248 and 300 nm) to assess purity of chromatographic peaks of ATV. The method was linear between 0.05 and 10 mg/L. Interday CV% ranged from 5% for atazanavir concentrations > 0.80 mg/L to 9% for a concentration of 0.15 mg/L. The lower limit of quantification (LOQ) of the assay was 0.02 mg/L. Atazanavir trough concentrations below the limit of quantification were fixed at LOQ/2 in the modeling process, which is one of the methods suggested by Beal (13).

Population pharmacokinetic modeling

Population approach was used to analyse atazanavir plasma concentrations. Non-linear mixed effects modeling implemented in NONMEM VII software (14) (Icon Development Solutions, Ellicott City, MA, USA) was used to identify the structural pharmacokinetic model and significant covariates that best described the data, and to estimate population PK parameters, as well as interindividual and residual variability. Composite methods based on modern algorithms was performed within the NONMEM estimation procedure: for each run, the stochastic approximation expectation maximization algorithm (SAEM) was first used, and
results of the SAEM estimation were then used as initial parameters to the Monte Carlo
Importance sampling method (14). Analysis and post-processing of NONMEM results were
performed using the R package for NONMEM (15) (RFN, version 2008a, Saik Urien, Paris,
France) and the Matlab software (version 2011b, The MathWorks, Natick, MA, USA).
We assumed log-normal distribution of the random parameters. An exponential error model
was used to describe residual variability. Various structural and absorption models were
investigated. Once the best base model had been identified, the influence of each available
covariate on PK parameters was investigated. The likelihood-derived objective function
calculated by NONMEM was used to assess goodness-of-fit of candidate models. In addition,
mean error of prediction and mean absolute error of prediction were used to assess predictive
performance. Plots of population predictions versus observed concentrations, individual
predictions versus observed concentrations and residuals were also examined as graphical
model diagnostics. In addition, visual predictive check (16) was performed, by simulating
1000 replicates based on the final model and corresponding parameters (including
interindividual and residual variability) and examining the agreement between model-based
simulated data and observed ATV concentrations.
Individual PK parameters of the final model, obtained by Bayesian estimation in NONMEM,
were then imported into the Matlab software to simulate the time-course of ATV plasma
concentrations of each patient at the steady state and calculate various indexes of drug
exposure, including the area under the concentration-time curve (AUC0-24), AUC above the
target concentration of 0.15 mg/L (AUCtarget), daily time during which ATV concentration
remains above the target concentration of 0.15 mg/L (Ttarget), and the predicted steady-state
trough concentration (Ctrough). For patients who received twice daily uATV, a 24 hour-profile
with two doses administered at 0 and 12 h was simulated to calculate AUC0-24, AUCtarget, and
Ttarget. The selection of the target Ctrough of 0.15 mg/L was based on a previous PK/PD study
Predicted rather than observed ATV C_{trough} values were used in the subsequent pharmacodynamic analysis because predicted values were available for all subjects, while a few observed values were missing (n=3) or reported as below the quantification limit (n = 4). In addition, individual predicted concentrations correlated well with observed concentrations (see the results section).

**Pharmacodynamic analysis**

First, individual pharmacokinetic parameters of the final model, indexes of drug exposure, and uATV dosage frequencies were statistically compared between patients who experienced virological failure and those without failure. The Mann-Whitney-Wilcoxon non-parametric test was used for continuous variables, while the Fisher’s exact was used for ordinal variables. Because multiple comparisons were performed, the statistical significance was fixed at 0.005 at this step.

Then, we explored the relationship between patients’ exposure to uATV and virological outcome after the switch. Univariate and multivariate logistic regression were performed using the Statview software (version 5.0, SAS Institute Inc., Cary, NC, USA) to identify pharmacokinetic variables influencing the probability of virological failure. The influence of each variable on the probability of virological failure was assessed by the likelihood ratio test (18). In this test, the difference denoted D is assumed to follow a chi-squared distribution:

\[
D = 2(\log L_{(alt)} - \log L_{(base)})
\]

where L is the likelihood, \( \log L_{(alt)} \) is the log-likelihood of the alternative (augmented) model, and \( \log L_{(base)} \) is the log-likelihood of the base model. Statistical significance was set at 0.05 with the appropriate degrees of freedom. Variables that were significant in the univariate
analysis were then tested in a multivariate model. The final model was identified, by forward addition, using again the likelihood ratio test as goodness-of-fit criterion. Statistical significance was set at 0.01 in the final model selection. As a limited number of failure events were observed in this study, lower than usual statistical significance levels were selected in order to control the number of events per variable. It has been shown that a low number of events per variable may negatively affect the estimation of the regression coefficient in logistic regression analysis (19).
Results

Characteristics of the study population

Fifty-eight patients were included in the study. Among those, seven patients received two different uATV-based regimens and one received four different uATV-based regimens. As those patients met the inclusion criteria for each drug regimen that they received, a total of 69 uATV-based regimens were available for the PK/PD analysis.

Demographic and treatment characteristics of the study population are presented in Table 1. In 25 cases, uATV was introduced as a switch from ritonavir-boosted ATV. The mean duration of the 69 uATV-based treatments was 16 ± 14 months (minimum, 1; maximum, 74).

The various uATV dosage regimens were as follows: 300 mg once daily (n=4), 400 mg once daily (n=22), 600 mg once daily (n=1), 200 mg twice daily (n=39), and 300 mg twice daily (n=3).

Seven patients experienced virological failure during their uATV-based regimen. Overall, their demographic and treatment characteristics were similar to those of patient without failure, except the dosing schedule. A tenfold failure rate was observed in patients under once daily uATV (6/27, 22%) compared with patients who received twice-daily uATV (1/42, 2.4%). This point is further discussed in the pharmacodynamic analysis.

Population pharmacokinetic modeling

One hundred and twenty-eight ATV concentrations were available for the pharmacokinetic analysis (mean, 1.86 measured concentrations per patient). Data included 66 trough (pre-dose) concentrations, 43 concentrations measured 3 hours after the dose, and 19 concentrations measured at another time-point.

A one-compartment model with linear elimination, fixed absorption lag-time, and mixture absorption best described ATV concentrations. Population parameter values of the final PK
model are shown in Table 2. The absorption lag-time was fixed at 0.9 h, in accordance with
the result from a population PK study with rich data (20). As a consequence of the mixture
model of absorption, two sets of population values are provided for F and Ka parameters. The
other pharmacokinetic parameters of the model were ATV plasma clearance (CL), volume of
distribution (Vd), proportion of regular absorbers, and the regression coefficient for the
influence of body weight on ATV clearance ($\theta_{BW}$).

For the mixture model of drug absorption, we assumed that there were two subpopulations of
absorbers in the study population, namely regular and low absorbers. Regular absorbers had a
mean oral bioavailability (F) and an absorption rate constant (Ka) both fixed at 1. Low
absorbers had mean values of parameters F and Ka both fixed at 0.4. Population means of F
and Ka were fixed because concentration data were insufficient to estimate them properly.
The initial absorption parameter values for regular and low absorbers were selected from
previous works (11, 21). Various combinations of fixed parameter values were tested for the
low absorber group and those indicated above provided the best fit. The addition of the
mixture model of ATV absorption was associated with a 27-point decrease in NONMEM
objective function value. Body weight was the only covariate that significantly influenced
ATV plasma clearance.

Figure 1 shows observed ATV concentrations versus model predictions based on population
parameter values and individual Bayesian posterior parameter values (B). Model-based
predictions correlated well with observed ATV concentrations, with regression equations as
follows: population predictions, $y = 0.95x + 0.14$, $r^2 = 0.73$; individual predictions, $y = 1.08x$
$-0.03$, $r^2 = 0.97$. Mean errors of prediction were $0.10 \pm 0.49$ mg/L and $-0.04 \pm 0.18$ mg/L,
while the mean absolute errors of prediction were $0.31 \pm 0.39$ and $0.09 \pm 0.15$ mg/L for
population and individual predictions, respectively. The plot of weighted residuals versus time
and the visual predictive check depicted in Figure 2 and Figure 3, respectively, also show
acceptable model performance. Limited shrinkage was observed for model parameters, which indicated that data were sufficiently informative at the individual level (22). The percent shrinkage values estimated by the SAEM algorithm for random effects ($\eta$-shrinkage) were as follows: CL, 28% (regular absorbers), 3% (low absorbers); Vd, 16% (regular absorbers), 9% (low absorbers); $K_{a,reg}$, 31%; $K_{a,low}$, 23%.

**Pharmacodynamic analysis**

Individual pharmacokinetic parameters and various atazanavir exposure data are presented in Table 3. Patients who experienced virological failure had significantly lower absorption rate constant $K_a$ ($p = 0.002$), AUC ($p = 0.001$), and AUC above the target concentration of 0.15 mg/L ($p = 0.002$) than patients without failure. In addition, the proportion of low absorbers (100% versus 50%, $p = 0.014$) and the proportion of once daily atazanavir administration (86% versus 34%, $p = 0.012$) were significantly higher in patients who experienced virological failure than in patients without failure.

Results of the logistic regression analysis are summarized in Table 4. In the univariate analysis, four continuous variables, $K_a$, AUC$_{0-24}$, T$_{target}$, C$_{trough}$, and one ordinal variable, the once daily administration, were identified as significant predictors of virological failure. In the subsequent multivariate analysis, only the absorption rate constant $K_a$ and estimated C$_{trough}$ significantly and independently influenced the probability of virological failure. For both variables, the probability of virological failure significantly increased when the value decreased. Of note, an alternative two-variable regression model, including $K_a$ ($p = 0.0004$) and T$_{target}$ ($p = 0.013$) was also identified, although the $p$-value for the T$_{target}$ variable fell short of statistical significance. One may be surprised by the very low odd-ratio values shown in Table 4 for the two variables of the final model. However, one should remind that the odd-ratio is the slope parameter in the logit model, thus representing the change in the probability
of the outcome associated with a one-unit increase of the independent variable. Because a
one-unit variation in the absorption rate constant or in ATV trough concentrations is a very
large, unlikely interindividual variation (see Table 3), one may consider instead the effect of a
0.1 unit variation of $K_a$ and $C_{\text{trough}}$ (see footnotes of Table 4).

While the results of the logistic regression showed that ATV exposure was significantly
associated with virological outcome, the final model had limited predictive ability, with a $r^2$ of
0.42, positive predictive value of 60%, and negative predictive value of 94%.

**Discussion**

In this work, we used pharmacometric tools to analyze PK/PD data of unboosted atazanavir
from a cohort of “real life” HIV-infected patients. A special feature of the final PK model is
the mixture model used to describe ATV absorption. The pharmacokinetics of ATV is
classified by large interindividual variability, especially in the absorption process.

Colombo *et al.* reported a mean absorption rate constant ($K_a$) of 0.41 h$^{-1}$, with an
interindividual variability of 122% (expressed as coefficient of variation, CV) (20). In another
population PK study, Solas *et al.* found a mean $K_a$ of 1.05 h$^{-1}$, with a CV of 156% (23). Other
works have suggested that the pharmacokinetics of ATV should not be considered as
homogeneous and that mixture models may be a relevant approach to describe ATV
pharmacokinetics. In an early study from ATV manufacturer, O’Mara *et al.* used a mixture
model with two subpopulations for the absorption rate constant ($K_a$) and volume of
distribution of the central compartment (11). In a recent study, a mixture model was also used
to accommodate differences observed in ATV exposure between subjects, with two
subpopulations for the three absorption parameters, $K_a$, lag-time and bioavailability $F$ (21).
In our study, because data available in the absorptive phase were very sparse, the absorption parameter could not be accurately estimated. As a consequence, we put strong constraints on the absorption parameters, fixing the fixed effects for Ka, F and lag-time, and setting no random effects for F and lag-time. In spite of this limitation, the mixture model with two subpopulations for Ka and F much improved the fit. Interestingly, despite differences in study design, data, and final PK models, the proportion of high and low exposure subjects showed remarkable agreement across studies. We found an estimated 49% proportion of regular absorbers, while O’Mara et al. and Andrade et al. reported proportions of high exposure subjects of 48% and 51%, respectively (11, 21). This mixture model may be viewed as a surrogate to accommodate the influence of unobserved variables such as adherence or food intake on ATV exposure.

In the pharmacodynamic analysis, a significant relationship was found between ATV exposure and virological failure. Two pharmacokinetic indexes estimated from the PK model were associated with the outcome, the absorption rate constant Ka and ATV trough concentration. While this variable was not selected in the final logistic regression model, it is interesting to note that all patients who experienced virological failure were identified as low absorbers by the mixture PK model.

Several studies have reported a significant relationship between ATV exposure and virological response. In an early in vitro study, Drusano and colleagues found that time greater than threshold (time > 4 x EC50, the viral 50% effective concentration) was the pharmacodynamic variable linked with atazanavir antiviral effect (24). O’Mara and colleagues first reported a relationship between atazanavir AUC and the log drop in HIV load in a phase II study (11) Later, another unpublished study from the manufacturer reported a significant association between ATV Ctrough and the probability of HIV load < 400 as well as < 50 copies/ml after 48 weeks of treatment in treatment-naive patients (25). Gonzalez de
Requena and colleagues found a similar relationship between ATV $C_{\text{trough}}$ and virological response at 12 weeks in ATV-naive patients and they proposed a cut-off value of 0.15 mg/L for ATV $C_{\text{trough}}$ (17). Others groups used the genotypic inhibitory quotient (GIQ), defined as atazanavir trough concentration divided by the number of protease inhibitor-associated mutations as a PK/PD index and reported a significant relationship between the GIQ and virological response (26-28). Reported cut-off values of GIQ were remarkably consistent across published studies, ranging from 183 to 230 ng/mL (0.183 – 0.230 mg/L) per mutation. The inhibitory quotient was not explored in this study, because data on PI-associated mutations were not available for all subjects in the cohort. Our results are in agreement with those from Bertz and Gonzalez de Requena (17, 25), although neither the suggested target $C_{\text{trough}}$ of 0.15 mg/L nor other indexes derived from it (i.e. $AUC_{\text{target}}$ and $T_{\text{target}}$) were found to be significant predictors of virological response in the final model.

Efficacy was the main outcome of this cohort PK/PD study. However, a weak but significant positive correlation was found between estimated ATV $C_{\text{trough}}$ and unconjugated bilirubin levels ($r^2 = 0.11, p = 0.006$, data not shown), as expected from previous reports (11, 17, 20). This study results also question the optimal dosage regimen of uATV. Once daily ATV administration was more frequent in patients who experienced virological failure than in patients without failure (see Table 3). In addition, the estimated ATV $C_{\text{trough}}$ values in patients who were administered uATV once daily ($0.18 \pm 0.17$ mg/L, $n = 27$) were lower than those in patients who received twice daily uATV ($0.36 \pm 0.21$ mg/L, $n = 42$), a statistically significant difference ($p < 0.001$, Mann-Whitney test). This observation is in agreement with the results from a pharmacokinetic study which examined the consequence of switching from unboosted ATV 400 mg once daily to 200 mg twice daily in ten stable patients who were co-administered tenofovir and emtricitabine (29). The geometric means of ATV $C_{\text{trough}}$ were 0.14 mg/L and 0.31 mg/L for the 400 mg once daily and 200 mg twice daily regimens, respectively.
Intracellular ATV trough concentrations were also increased after the switch. As our study and others have identified ATV C_{trough} as a significant predictor of virological failure, twice daily uATV administration appears to optimize drug exposure compared with the FDA approved unboosted once-daily regimen. Although limited, available data indicate that average C_{trough} associated with the uATV 200 mg twice daily regimen are much lower than the 0.85 mg/L cut-off associated with hyperbilirubinemia (17), which suggests favorable tolerance. Further research is necessary to determine the optimal dosage design of uATV.

This study has several limitations that should be considered when interpreting the results, some of them being inherent to cohort studies. For example, food intake and adherence, which may significantly alter ATV exposure, could not be precisely assessed in such a study. Although the antiretroviral backbone was not controlled in this study, the vast majority of patients received similar antiretroviral regimens, based on two or more NRTIs in addition to uATV (see Table 1). Important pharmacodynamic variables such as susceptibilities of HIV isolates (EC_{50}) and binding to alpha-1 acid glycoprotein (24) were not available. As a consequence, a full mechanistic PK/PD modeling approach could not be carried out. Data available for the pharmacokinetic analysis were relatively sparse. However, an adaptive model building was performed, and the final model parameters were estimated with acceptable precision. Also, the final model adequately described the data, with good predictive performance.

In conclusion, a population pharmacokinetic model, including a mixture model of absorption adequately described ATV concentrations in a cohort of HIV-infected patients who were administered unboosted atazanavir. Significant differences in ATV pharmacokinetics and regimens have been observed between patients who experienced virological failure under uATV and those who did not. Atazanavir absorption rate constant and trough concentration significantly influenced the probability of virological failure in the logistic regression.
analysis. This work also suggests that twice daily administration of unboosted atazanavir may optimize drug therapy.
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based differences in atazanavir pharmacokinetics in subjects treated with didanosine, emtricitabine, and atazanavir in the AIDS clinical trials group (ACTG) prospective evaluation of antiretrovirals in resource limited settings (PEARLS) study. 18th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, MA, USA.


# Table 1

Demographic and treatment characteristics of patients included in the study

<table>
<thead>
<tr>
<th></th>
<th>No failure (n=62)</th>
<th>Virological Failure (n=7)</th>
<th>Total (n=69)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>50 ± 9.7</td>
<td>47 ± 9.4</td>
<td>49 ± 9.6</td>
</tr>
<tr>
<td>Sex ratio male/female (%)</td>
<td>46/16 (74%)</td>
<td>4/3 (57%)</td>
<td>50/19 (72%)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>69 ± 12</td>
<td>70 ± 13</td>
<td>69 ± 12</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>93 ± 25</td>
<td>84 ± 23</td>
<td>92 ± 24</td>
</tr>
<tr>
<td>(ml/min/1.73 m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal impairment*</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dosing frequency, once daily/twice daily (% of once daily administration)</td>
<td>21/41 (34%)</td>
<td>6/1 (86%)</td>
<td>27/42 (39%)</td>
</tr>
<tr>
<td>Drug-drug interactions</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>increasing ATV exposure</td>
<td>1 (1.6%)</td>
<td>1 (14%)</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>decreasing ATV exposure</td>
<td>28 (45%)</td>
<td>3 (43%)</td>
<td>31 (45%)</td>
</tr>
<tr>
<td>Time since HIV diagnosis (years)</td>
<td>11 ± 6</td>
<td>11 ± 5</td>
<td>11 ± 6</td>
</tr>
<tr>
<td>Time since first antiretroviral treatment (years)</td>
<td>8 ± 5</td>
<td>6 ± 4</td>
<td>8 ± 5</td>
</tr>
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<td>Antiretroviral companion drugs</td>
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<td></td>
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<tr>
<td>≥ 2 NRTIs</td>
<td>57 (92%)</td>
<td>7 (100%)</td>
<td>64 (93%)</td>
</tr>
<tr>
<td>InSTI + NRTIs</td>
<td>5 (8%)</td>
<td>0 (0%)</td>
<td>5 (7%)</td>
</tr>
</tbody>
</table>
a Initial body weight at the treatment onset

b Initial GFR estimated by the abbreviated MDRD equation (data available for 61 subjects, 5 with failure and 56 without failure)

c Defined as estimated GFR ≤ 60 ml/min

Data are given as mean ± standard deviation unless otherwise indicated

Abbreviations: NRTI, nucleoside (or nucleotide) reverse transcriptase inhibitor; InSTI, Integrase strand transfer inhibitor
Table 2
Pharmacokinetic parameters of the final model estimated by NONMEM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population typical value (RSE)</th>
<th>Interindividual variability(^a) (RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>13.4 (8.4%)</td>
<td>24.9 (40.7%)</td>
</tr>
<tr>
<td>(\theta_{BW} \text{ (L.h}^{-1}\text{.kg}^{-1}))(^b)</td>
<td>0.00936 (41.3%)</td>
<td></td>
</tr>
<tr>
<td>Vd (L)</td>
<td>71.1 (12.0%)</td>
<td>47.0 (29.7%)</td>
</tr>
<tr>
<td>Absorption lag-time (h)</td>
<td>0.9 (fixed)</td>
<td></td>
</tr>
<tr>
<td>(K_{a\text{reg}} \text{ (h}^{-1}))</td>
<td>1.0 (fixed)</td>
<td>50 (fixed)</td>
</tr>
<tr>
<td>(K_{a\text{low}} \text{ (h}^{-1}))</td>
<td>0.4 (fixed)</td>
<td>68.7 (89.6%)</td>
</tr>
<tr>
<td>(F_{\text{reg}})</td>
<td>1.0 (fixed)</td>
<td></td>
</tr>
<tr>
<td>(F_{\text{low}})</td>
<td>0.4 (fixed)</td>
<td></td>
</tr>
<tr>
<td>Proportion of regular absorbers</td>
<td>0.49 (21.6%)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Interindividual variability is expressed as percent coefficient of variation (CV%). No interindividual variability was set for the absorption lag-time and the bioavailability parameters, \(F_{\text{reg}}\) and \(F_{\text{low}}\).

\(^b\) The influence of body weight (BW) on the typical value of ATV mean clearance (\(\mu_{CL}\)) was coded as follows: \(\mu_{CL} = \theta_1 \cdot (1 + \theta_{BW} \cdot (BW - 67))\), where 67 was the median body weight in the study population.
Table 3
Comparison of pharmacokinetic parameter values and various exposure data in patients with and without virological failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No failure (n=62)</th>
<th>Virological failure (n=7)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/h)</td>
<td>13.3 ± 2.6</td>
<td>15.3 ± 2.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>74.7 ± 24.6</td>
<td>81.5 ± 19.4</td>
<td>0.31</td>
</tr>
<tr>
<td>Ka (h&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>0.75 ± 0.28</td>
<td>0.38 ± 0.20</td>
<td>0.002</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (mg.h.L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>22.4 ± 11.2</td>
<td>10.3 ± 2.1</td>
<td>0.001</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;target&lt;/sub&gt; (mg.h.L&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>18.9 ± 11.1</td>
<td>7.1± 1.9</td>
<td>0.002</td>
</tr>
<tr>
<td>T&lt;sub&gt;target&lt;/sub&gt; (h)</td>
<td>22.9 ± 2.5</td>
<td>19.9 ± 4.9</td>
<td>0.045</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt; (mg/L)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.31 ± 0.22</td>
<td>0.11 ± 0.08</td>
<td>0.012</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt; &lt; 0.15 mg/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17 (27%)</td>
<td>4 (57%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Low absorbers</td>
<td>31 (50%)</td>
<td>7 (100%)</td>
<td>0.014</td>
</tr>
<tr>
<td>Once daily administration</td>
<td>21 (34%)</td>
<td>6 (86%)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mann-Whitney test (continuous variables) or Fisher exact test (ordinal variable)

<sup>b</sup> Individual trough concentration estimated from the pharmacokinetic model
Table 4

Logistic regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CL</td>
<td>1.34</td>
<td>0.99 – 1.82</td>
<td>0.053</td>
</tr>
<tr>
<td>Ka</td>
<td>0.0034</td>
<td>4.9E-5 – 0.24</td>
<td>0.0008</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt;</td>
<td>0.66</td>
<td>0.43 – 1.016</td>
<td>0.0003</td>
</tr>
<tr>
<td>T&lt;sub&gt;target&lt;/sub&gt;</td>
<td>0.79</td>
<td>0.64 – 0.97</td>
<td>0.03</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt;</td>
<td>3.0E-4</td>
<td>1.4E-7 - 0.63</td>
<td>0.005</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt; &lt; 0.15 mg/L</td>
<td>3.53</td>
<td>0.71 – 17.44</td>
<td>0.12</td>
</tr>
<tr>
<td>Once daily administration</td>
<td>11.7</td>
<td>1.3 – 103.8</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Final multivariate model</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ka</td>
<td>4.2E-4</td>
<td>10E-7 – 0.18</td>
<td>0.008</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt;</td>
<td>5.6E-6</td>
<td>8.1E-11 – 0.39</td>
<td>0.005</td>
</tr>
</tbody>
</table>

* Likelihood ratio test, p-value associated with the exclusion of each independent variable in the model

Note: The odd-ratio represents the variation of the probability of virological failure associated with a one-unit increase of the independent variable. The OR associated with a 0.1-unit change of the variable are 0.57 and 0.44 in the univariate models, 0.46 and 0.30 in the multivariate model, for Ka and C<sub>trough</sub>, respectively

Abbreviations: OR, odd-ratio, CI, confidence interval
Figure 1. Observed atazanavir concentrations versus model predictions. Left panel, open circles, population predictions; right panel, filled circles, individual predictions based on Bayesian posterior parameters. The solid line is the line of identity (y=x).
Figure 2. Weighted residuals versus time post-dose.

The dashed line is the regression line.
Figure 3. Visual predictive check from the final pharmacokinetic population model.

Open circles, observed atazanavir concentrations; solid line, median of simulated concentrations; dashed lines, 5th and 95th percentiles of simulated concentrations.

The observed trough levels at 12h (twice daily regimen) and 24h (once daily regimen) post-dose were duplicated for ease of graphical display.