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# A pilot study on the efficacy, pharmacokinetics and safety of atazanavir in patients with end-stage liver disease

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***Objectives*: Antiretroviral combinations including atazanavir are currently not recommended in HIV-infected patients with end-stage liver disease (ESLD). The objective of our study was to evaluate efficacy, pharmacokinetics and safety of unboosted atazanavir in HIV-infected patients with ESLD screened for orthotopic liver transplantation ($OLT_x$).**

***Patients and methods*: Single-arm, 24 week pilot study. Atazanavir-naive patients undergoing highly active antiretroviral therapy were switched to atazanavir 400 mg/day plus two non-thymidine nucleoside reverse transcriptase inhibitors.**

***Results*: Fifteen patients (10 males and 5 females) were included. In the study period, 2 patients were transplanted and 10 completed 24 weeks of atazanavir treatment. Median area under the concentration–time curve at week 4 was 19 211 ng·h/mL (IQR = 8959–27 500). At week 24, median atazanavir trough concentrations ($C_{trough}$) per patient calculated across the study were above the minimum effective concentration (MEC = 100 ng/mL) in 8 of 10 subjects. Atazanavir $C_{trough}$ time-point values were always above the MEC in five patients. The other three subjects experienced only one determination below the MEC, with median atazanavir $C_{trough}$ levels across the study being above the MEC in two of them. At 8 of 11 time-points when atazanavir and proton pump inhibitors (PPIs) were co-administered and at 16 of 19 time-points in which patients had a concomitant tenofovir association, atazanavir $C_{trough}$ was above the MEC.**

***Conclusions*: Unboosted atazanavir showed a favourable pharmacokinetic profile and was able to maintain or gain immuno-virological eligibility for $OLT_x$ in all patients. Limited biochemical toxicities (including unconjugated hyperbilirubinaemia) and allowance of concomitant administration of tenofovir and PPIs were observed.**

Keywords: HIV, therapeutic drug monitoring, unboosted protease inhibitors, liver insufficiency, drug–drug interactions

## Introduction

Since 1996, the availability of highly active antiretroviral therapy (HAART) for HIV-infected patients has resulted in a remarkable decrease in HIV-related morbidity and mortality.[1] This decline has been accompanied by a relative increase in morbidity and mortality associated with chronic hepatic impairment.[2,3] End-stage liver disease (ESLD), which is largely the

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result of hepatitis C virus (HCV) infection, now accounts for up to 50% of deaths among persons with HIV infection.[2]

Hepatic disease can affect drug metabolism,[4,5] and HIV/HCV co-infected patients are at an increased risk of drug toxicity, which has been attributed to both changes induced by chronic viral infections and the impairment of the pathways involved in liver metabolism of antiretroviral agents (ARVs).[6] The cytochrome P450 (CYP450) family of enzymes is responsible for the metabolism of most antiretroviral drugs, particularly protease inhibitors (PIs) as well as non-nucleoside reverse transcriptase inhibitors (NNRTIs) and integrase inhibitors.

Metabolic efficacy of the CYP450 enzyme family progressively decreases along with worsening liver function,[7] producing an increase in plasma concentration of ARVs[6,8–13] and, ultimately, the potential for serious hepatic toxicities and interference with concomitant treatments.[14–16] On the other hand, a beneficial long-term effect of HAART in ESLD has been supported in some studies,[17] suggesting a reduction in liver-related mortality that outweighs the potential risks of drug hepatotoxicity.

Up to now, data on PI pharmacokinetics in patients suffering from chronic liver disease are lacking.[6,8–13,18–21] Recommendations about PI use and dose adjustments in subjects with hepatic impairment have been issued,[22] and antiretroviral combinations including atazanavir [Reyataz; Bristol–Myers Squibb (BMS), Princeton, NJ, USA] are currently not recommended in patients with HIV infection suffering from ESLD.[23]

A pilot study to evaluate efficacy, pharmacokinetics [trough concentration ($C_{trough}$) levels, area under the concentration–time curve (AUC) and maximum concentration ($C_{max}$) levels] and safety of unboosted atazanavir was conducted in patients with HIV infection suffering from ESLD. The secondary objective of the study was to analyse any significant drug–drug interaction between atazanavir and tenofovir, proton pump inhibitors (PPIs) and $H_2$-receptor antagonists (anti-$H_2$). Patients were recruited at the Transplant Centre of the University of Modena and Reggio Emilia among HIV-infected individuals evaluated for orthotopic liver transplantation ($OLT_x$) in accordance with the Italian National Liver Transplant Programme.

## Patients and methods

### *Study design, patients and study treatment*

Single centre, 24 week, open-label pilot study in HIV-infected individuals with ESLD receiving an atazanavir-based HAART regimen from September 2005 to September 2006.

Consecutive adult patients with HIV infection and ESLD, evaluated for $OLT_x$ according to the Italian National Liver Transplant Programme for HIV-infected patients, were screened at the Transplant Centre of the University of Modena and Reggio Emilia. ESLD was defined as a Child–Pugh score $\geq$B7, hepatic cirrhosis documented either by liver biopsy (Ishak stage 4 fibrosis) or clinical and ultrasonographic diagnostic criteria (liver surface nodularity, caudate lobe hypertrophy and changes in hepatic venous flow) and at least one episode of liver decompensation.[24–26]

Patients with potential benefits of $OLT_x$ and no previous treatment with atazanavir and with no atazanavir-related major resistance mutations were switched at study entry from an NNRTI or a pharmacologically enhanced (boosted) PI to atazanavir 400 mg once daily, maintaining their nucleoside reverse transcriptase inhibitor (NRTI) backbone if plasma HIV-RNA viral load (VL) was undetectable (<50 copies/mL) or optimizing the NRTIs according to plasma HIV genotypic resistance test.

In accordance with BMS Pharmaceuticals' warning on significant drug–drug interactions,[27] the protocol discouraged the use of PPIs and anti-$H_2$, if not strictly necessary, and collected pharmacokinetic data when atazanavir was concomitantly administered with these drugs. Dropout criteria were: $OLT_x$, death and atazanavir discontinuation. The study was authorized by the local Ethics Review Board and all subjects provided written informed consent prior to enrolment.

### *Data collection*

Baseline data included demographics (ethnic origin, gender and age), HIV characteristics (transmission risk factors, duration of HIV infection, HIV CDC classification, nadir CD4+ cell count, class type and exposure to antiretroviral therapy, plasma HIV genotypic resistance assay antecedent or concomitant to switching and current HAART) and ESLD history (aetiology, known duration of cirrhosis, HCV genotype, baseline serum HCV-RNA VL, previous cirrhotic decompensation episodes and presence of histologically documented hepatocellular carcinoma). Follow-up data collected at weeks 0, 2, 8, 16 and 24 included: (i) anthropometric characteristics [weight, height and body mass index (BMI)]; (ii) HIV parameters (plasma HIV-RNA VL, CD4+ cell count, immuno-virological eligibility for $OLT_x$ and plasma HIV genotypic resistance assay when VL was detectable); (iii) ESLD indexes [Child–Pugh score, the model for ESLD (MELD) score and the aspartate aminotransferase-to-platelet ratio index (APRI) score]; (iv) liver and kidney biochemistry tests [total and unconjugated bilirubin (TBIL and UBIL, respectively), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), alkaline phosphatase (ALKP), international normalized ratio (INR), albumin (ALB) and glomerular filtration rate with the modification of diet in renal disease (MDRD) calculation]; (v) concomitant treatments (PPIs and anti-$H_2$); (vi) relevant clinical events [death, liver decompensation and virological failure (defined as plasma HIV-RNA VL $\geq$1000 copies/mL and grade III–IV pharmacological toxicities)]; and (vii) adherence evaluation (assessed with unstructured questionnaire and pill-counts).

### *Sample collection for therapeutic drug monitoring (TDM)*

Pharmacokinetic assays were centralized at the Pharmacology Clinic of the Antiretrovirals Laboratory, Infectious Diseases Department, University of Turin, Italy. Plasma atazanavir concentration was measured at the end of the dosing interval (trough level) at each time-point of follow-up. Moreover, at week 4, additional samples (immediately before and 1.5, 3, 5, 7 and 24 h after atazanavir intake, respectively) were obtained in order to evaluate $C_{max}$ levels and AUC. Plasma samples were separated, inactivated in a bath at 58°C for 35 min and then frozen at −20°C until analyses were performed. Plasma atazanavir concentrations were measured by a modified HPLC method with UV detection validated over the concentration range of 100–5000 ng/mL, using 0.5 mL of plasma.[28] The efficacy of extraction of atazanavir from human plasma was evaluated as the percentage of recovery equal to 102% ± 5 SD. The intraday precision of the method used for dosing atazanavir was measured as relative standard deviation percentage (RSD%) that was 1% for a low quality control (QC) level, 10% for medium and 11% for high. The interday RSD% was 4% for low QC level, 10% for medium and 11% for high. The intraday accuracy rates ranged from 96% to 98% and the interday from 98% to 99%.

The sensitivity for atazanavir $C_{trough}$ level of our method was 40 ng/mL in the range of linearity. For statistical purposes, the $C_{trough}$ level below the limit of detection was fixed as half of the assay sensitivity (equal to 20 ng/mL). Pharmacokinetic analysis compared $C_{trough}$ levels of samples with the minimal effective concentration (MEC) value of unboosted atazanavir (suggested by BMS as being equal to 100 ng/mL) at any time-point. Drug interactions were evaluated analysing the proportion of patients with $C_{trough}$ levels above the MEC in the presence or absence of a concomitant administration of tenofovir, PPIs and anti-$H_2$ agents.

### *Outcome measures*

Efficacy outcomes for the study were the proportion of patients with plasma HIV-RNA VL below the limit of detection, CD4+ cell count changes from baseline and the proportion of patients immunovirologically eligible for $OLT_x$ with regard to the Italian National Liver Transplant Programme for people with HIV on HAART (stable CD4+ cell count $\geq$200 cells/mm$^3$ for at least 12 months and undetectable plasma HIV-RNA VL).[29]

For pharmacokinetic analyses, the main study outcome was AUC, $C_{max}$ and the proportion of patients with atazanavir $C_{trough}$ levels above the MEC.

Safety outcomes were: death; grade III–IV drug toxicities; changes in serum TBIL, UBIL, ALT, GGT, ALKP, INR and ALB; changes in Child–Pugh, APRI, MELD and MDRD scores; and capacity to tolerate HAART in the follow-up period.

Data concerning outcome variables from patients who did not complete 24 weeks were collected in the follow-up.

### *Statistical analysis*

Biochemical values (TBIL, UBIL, ALT, GGT, ALKP, INR and ALB) and CD4+ cell count were expressed as medians and interquartile ranges (IQRs). The changes from baseline were analysed for statistical significance using the Wilcoxon test. Differences in atazanavir $C_{trough}$ values between patients with/without concomitant treatment with tenofovir, PPIs and anti-$H_2$ agents at different study weeks were analysed using the Mann–Whitney *U*-test. In all the above analyses, a threshold of 0.05 was used for statistical significance. All the analyses were performed using the SPSS software.[30]

## Results

### *Subjects*

Fifteen consecutive patients were enrolled in the trial and 10 completed the study after a 24 week follow-up. A flow chart summarizing outcomes and dropouts of study participants is given in Figure 1.

All the 15 evaluable subjects (10 males and 5 females) were Caucasian adults with a median age of 44 years (IQR = 41–46). Median weights and heights were 70 kg (IQR = 52.5–80) and 171 cm (IQR = 164–179), respectively, with a median BMI of 23 (IQR = 20–25.5).

The route of transmission for HIV was intravenous drug use in 14 patients and heterosexual intercourse in the remaining patient. Twelve (80%) subjects had a baseline undetectable (<50 copies/mL) plasma HIV-RNA VL. In the remaining three viraemic subjects, plasma HIV genotypic resistance test did not show any major atazanavir mutation. Eleven patients (73%) had a baseline CD4+ cell count >200 cells/mm$^3$ (median value = 298 cells/mm$^3$; IQR = 197–322). The median nadir CD4+ cell count was 161 cells/mm$^3$ (IQR = 70–200).

Table 1 summarizes HIV data and concomitant treatments at study entry. Baseline data on ESLD, liver and kidney function tests are given in Table 2.

### *Efficacy measures*

Twelve patients (80%) had undetectable plasma HIV-RNA VL at enrolment; among the 10 subjects who completed the study, 9 had undetectable HIV-RNA VL at week 24 (90%) and 1 had a detectable but low VL (117 copies/mL). Median CD4+ cell count was 298 cells/mm$^3$ among enrolled patients at baseline and 340 cells/mm$^3$ among the 10 subjects who completed the

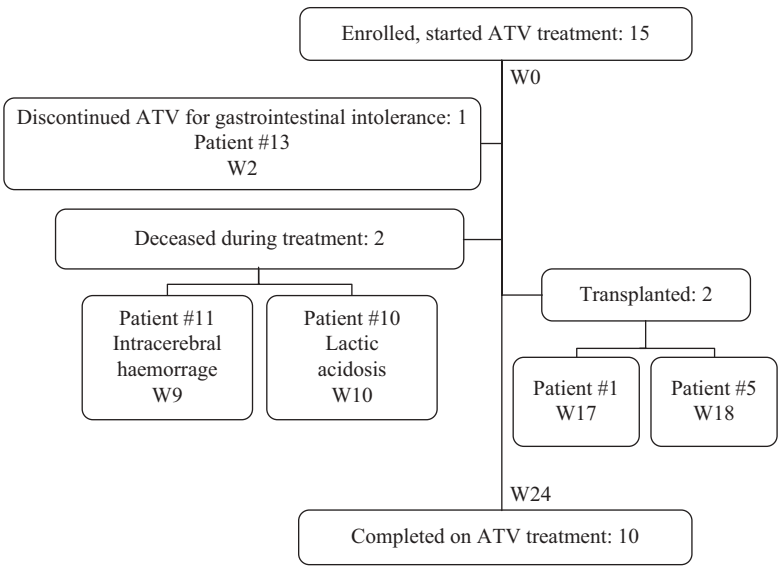


**Figure 1.** Flow chart of the study population with outcomes during the study.

**Table 1.** HIV infection history, baseline variables and concomitant treatments

| Case no. | HIV CDC | Baseline HIV genotypic assay[a] | Last HAART before switching[b] | Current HAART | Baseline HIV-RNA (copies/mL) | Baseline CD4+ (cells/mm$^3$) | $OLT_x$ eligibility | Type and daily dose of PPIs[c] | Use of anti-$H_2^d$ |
|---|---|---|---|---|---|---|---|---|---|
| 1 | B3 | | fosAPV + EFV + 3TC | ATV + 3TC + ABC | <50 | 164 | no | none | yes |
| 2 | A2 | | D4T + 3TC + TDF | ATV + 3TC + TDF | <50 | 241 | yes | omeprazole 20 mg QD | no |
| 3 | B2 | | SQV + 3TC + TDF | ATV + 3TC + TDF | <50 | 305 | yes | omeprazole 20 mg QD | no |
| 4 | C3 | | AZT + 3TC + ABC | ATV + 3TC + ABC | <50 | 148 | no | omeprazole 20 mg QD | no |
| 5 | B3 | | AZT + 3TC + ABC | ATV + 3TC + ABC | <50 | 303 | yes | none | yes |
| 6 | B3 | | ABC + 3TC + SQVr | ATV + 3TC + ABC | <50 | 387 | yes | none | no |
| 7 | B3 | | 3TC + TDF + NFV | ATV + FTC + TDF | <50 | 322 | yes | omeprazole 20 mg QD | no |
| 8 | C3 | | 3TC + TDF + NFV | ATV + 3TC + ABC | <50 | 307 | yes | none | no |
| 9 | B2 | PRO: 10V, 63P | D4T + TDF + NFV | ATV + FTC + TDF | 134 | 276 | no | lansoprazole 30 mg QD | no |
| 10 | A2 | PRO: 36I | DDI + TDF + LPVr | ATV + 3TC + ABC | 59 223 | 225 | no | none | no |
| 11 | B3 | PRO: L63C, A71T, I93L | TDF + D4T + 3TC | ATV + TDF + ABC | 144 | 103 | no | none | no |
| 12 | B3 | | TDF + D4T + 3TC | ATV + 3TC + TDF | <50 | 187 | no | lansoprazole 30 mg BID | no |
| 13 | B3 | | 3TC + TDF + NFV | ATV + 3TC + TDF | <50 | 739 | yes | none | no |
| 14 | B2 | | ABC + LPVr | ATV + 3TC + ABC | <50 | 370 | yes | omeprazole 20 mg QD | no |
| 15 | A3 | | TDF + 3TC + APV | ATV + 3TC + TDF | <50 | 298 | yes | rabeprazole 10 mg QD | no |

[a]PRO, protease genotype.
[b]Drug abbreviations: fosAPV, fosamprenavir; EFV, efavirenz; 3TC, lamivudine; ABC, abacavir; D4T, stavudine; SQV, saquinavir; SQVr, saquinavir/ritonavir; NFV, nelfinavir; FTC, emtricitabine; DDI, didanosine; LPVr, lopinavir/ritonavir; APV, amprenavir.
[c]Dosage abbreviations: QD, once-a-day; BID, twice-a-day.
[d]Anti-$H_2$, $H_2$-receptor agonists.



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**Table 2.** ESLD history and baseline liver and kidney biochemical tests

| Case no. | Aetiology of ESLD | HCC | Child–Pugh score | MELD score | APRI score | TBIL (mg/dL) | UBIL (mg/dL) | ALT (U/L) | GGT (U/L) | ALKP (U/L) | INR | ALB (mg/dL) | MDRD (mL/min) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | HCV | no | B9 | 18 | 8.9 | 4.57 | 1.33 | 116 | 157 | 309 | 1.44 | 3.13 | 78 |
| 2 | cryptogenic | no | B7 | 8 | 0.6 | 1.25 | 0.85 | 29 | 47 | 108 | 1.22 | 3.9 | 94 |
| 3 | HCV | no | B9 | 14 | 5.1 | 2.39 | 0.73 | 90 | 32 | 162 | 1.71 | 2.4 | 83 |
| 4 | HCV + alcohol | yes | C10 | 12 | 3 | 3.2 | 1.6 | 42 | 48 | 403 | 1.5 | 2.5 | 130 |
| 5 | HBV + HDV | yes | C10 | 18 | 5.9 | 4.3 | 2.3 | 88 | 164 | 688 | 1.38 | 2.7 | 133 |
| 6 | HCV | no | B7 | 13 | 2.5 | 1.91 | 0.68 | 40 | 61 | 206 | 1.39 | 3.8 | 99 |
| 7 | HBV + HCV + alcohol | no | B7 | 6 | 1 | 1.19 | 0.19 | 19 | 45 | 450 | 1.17 | 3.6 | 91 |
| 8 | HCV + alcohol | no | B8 | 22 | 2.1 | 9.3 | 2.5 | 47 | 26 | 453 | 1.68 | 3.3 | 77 |
| 9 | HBV + HDV + HCV | no | B8 | 13 | 6.4 | 1.94 | 1.15 | 102 | 105 | 196 | 1.56 | 3.3 | 101 |
| 10 | HCV | no | C10 | 18 | 9 | 2.9 | 1.79 | 68 | 70 | 324 | 1.12 | 2.1 | 57 |
| 11 | HBV + HCV | no | C10 | 31 | 12.8 | 16.42 | 5.4 | 77 | 16 | 267 | 3.4 | 3 | 64 |
| 12 | HBV + HDV + HCV | yes | B9 | 15 | 2 | 1.2 | 0.7 | 36 | 33 | 197 | 1.48 | 2.9 | 111 |
| 13 | HCV | no | C10 | 15 | 3.3 | 3.54 | 1.16 | 64 | 97 | 490 | 1.42 | 3.3 | 85 |
| 14 | HCV | no | B9 | 10 | 1.1 | 2.18 | 1.1 | 17 | 65 | 437 | 1.22 | 3 | 112 |
| 15 | HCV | no | B7 | 10 | 5.6 | 1.4 | 0.9 | 74 | 52 | 64 | 1.3 | 3.6 | 73 |

ESLD, end-stage liver disease; HCC, hepatocellular carcinoma; MELD, model for ESLD; APRI, aspartate aminotransferase-to-platelet ratio index; TBIL, total bilirubin; UBIL, unconjugated bilirubin; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; ALKP, alkaline phosphatase; INR, international normalized ratio; ALB, albumin; MDRD, glomerular filtration rate with the modification of diet in renal disease calculation; HCV, hepatitis C virus; HBV, hepatitis B virus; HDV, hepatitis D virus.

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study, indicating a small, although not significant, cell count increase during follow-up ($P = 0.386$).

At entry, 9 of 15 patients (60%) were immunologically and virologically eligible for $OLT_x$. Among the 10 subjects who completed the study, 9 (90%) were eligible for transplantation at week 24 and 1 remained ineligible. Among the patients who did not complete 24 weeks, two were transplanted (Case 1 at week 17, after having become eligible at week 8, and Case 5, eligible from enrolment, at week 18), two remained $OLT_x$-ineligible and died during the follow-up and one eligible patient discontinued atazanavir because of gastrointestinal intolerance. Two subjects (Cases 6 and 9) admitted to a transient lack of adherence to the study drug.

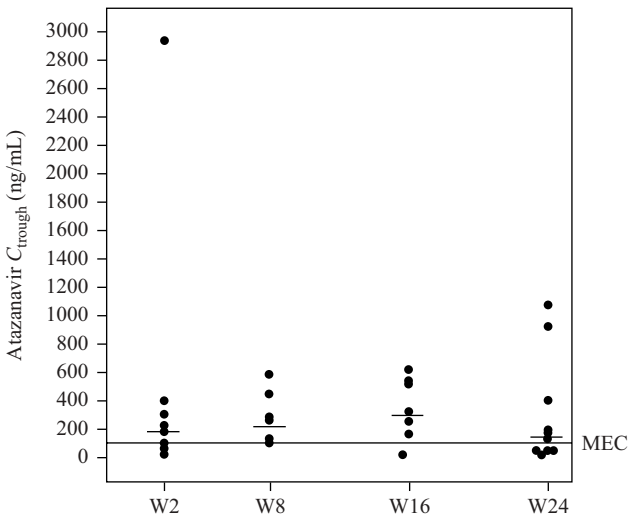


**Figure 2.** Atazanavir $C_{trough}$ levels at each time-point represented as individual and median values.

*Pharmacokinetic analysis*

Individual and median values of atazanavir $C_{trough}$ at any time-point of the follow-up period for the entire group of patients are represented in Figure 2.

Median atazanavir $C_{trough}$ values at different study weeks were 186 ng/mL at week 2 (IQR = 83.5–270.5), 197.5 ng/mL at week 8 (IQR = 109–448.5), 321 ng/mL at week 16 (IQR = 169–540) and 147.5 ng/mL at week 24 (IQR = 50–664). Table 3 shows patient AUC and $C_{max}$ at week 4 of the study, as well as median atazanavir $C_{trough}$ levels across the study. Four patients had atazanavir $C_{trough}$ levels below the MEC at week 24. Two of them, Cases 6 and 9, admitted episodes of intermittent non-adherence and had a transient HIV-RNA viraemic blip 1 month after the conclusion of the trial.

The role of concomitant treatment with tenofovir, PPIs or anti-$H_2$ agents was assessed by examining individual and median values for patients with and without such concomitant treatments at different study weeks.

Overall, in eight patients receiving concomitant tenofovir, median atazanavir $C_{trough}$ values were above the MEC at all study weeks (week 2: 228 ng/mL, IQR = 144–354.5; week 8: 450 ng/mL, IQR = 449–519; week 16: 540 ng/mL, IQR = 529–580.5; and week 24: 301 ng/mL, IQR = 87.25–794.5). Atazanavir $C_{trough}$ time-point values were always above the MEC in five patients. The other three subjects experienced only one determination below the MEC, but in these, median atazanavir $C_{trough}$ values across the study were above the MEC. Atazanavir $C_{trough}$ levels were above the MEC in 16 of the 19 total samples (84%) collected in the presence of a concomitant administration of atazanavir and tenofovir.

In the study period, six patients had concomitant PPI administration in at least one study visit. In this group, median atazanavir $C_{trough}$ values were above the MEC at week 2 (307 ng/mL), week 8 (120 ng/mL) and week 16 (254 ng/mL), but not at week 24 (50 ng/mL). Overall, atazanavir $C_{trough}$ levels were above the

**Table 3.** AUCs and $C_{max}$ levels at week 4 and median atazanavir $C_{trough}$ levels across the study

| Case no. | AUC week 4 (ng·h/mL) | $C_{max}$ week 4 (ng/mL) | Median (IQR) $C_{trough}$ W2–W8–W16–W24 (ng/mL) |
|---|---|---|---|
| 1 | 19 211 | 243 | 76.5 (64.75–88.25) |
| 2 | 2693 | 1804 | 133 (100–166) |
| 3 | 41 122 | 3483 | 178.5 (114.25–242.75) |
| 4 | 1316 | 117 | 114.5 (83–136) |
| 5 | 7537 | 891 | 261 (247.5–274.5) |
| 6 | 27 500 | 4003 | 78.5 (20–159) |
| 7 | 10 904 | 1082 | 254 (179.5–328.5) |
| 8 | 9151 | 1087 | 120 (85–187) |
| 9 | 37 847 | 2998 | 588 (319–604.5) |
| 10 | 8959 | 238 | 222 (204–240) |
| 11 | NA | NA | 402 |
| 12 | 54 680 | 4024 | 808 (517.5–1542.25) |
| 13 | NA | NA | 228 |
| 14 | 22 546 | 1419 | 140.5 (108.25–207.75) |
| 15 | 22 358 | 2480 | 483 (381.75–619.75) |
| Total median (IQR) values | 19 211 (8959–27 500) | 1419 (891–2998) | 222 (126.5–331.5) |

NA, not available.

MEC in 8 of 11 samples (73%) collected in the presence of a concomitant administration of atazanavir and PPIs. Three patients always had atazanavir $C_{trough}$ values above the MEC at any time-point. In the remaining three patients, atazanavir $C_{trough}$ levels were below the MEC only once (one at week 2 and two at week 24, respectively), but none experienced a viro-immunological or clinical failure during the follow-up. In two of them, median atazanavir $C_{trough}$ values across the study were above the MEC.

Eight patients had concomitant anti-$H_2$ administration in at least one study visit. In this group, median atazanavir $C_{trough}$ levels were at or above the MEC at all study weeks (week 2, 100 ng/mL; week 8, 288 ng/mL; week 16, 529 ng/mL; week 24, 184.5 ng/mL). Atazanavir $C_{trough}$ time-point values were always above the MEC in five patients, while the other three subjects experienced only one determination below the MEC, with median atazanavir $C_{trough}$ levels across the study above the MEC in two of them. Overall, in 17 of 20 samples (85%) collected in the presence of atazanavir and anti-$H_2$ co-administration, atazanavir $C_{trough}$ values were above the MEC.

### *Safety assessment*

Two patients died during the follow-up. The first death (Case 11) occurred at week 9 from intracerebral haemorrhage, and the second (Case 10) at week 10 from lactic acidosis. Two subjects reported grade III toxicities (diarrhoea), which in one case (13) was responsible for atazanavir discontinuation at week 2.

In patients completing the study, no significant changes in ALT, GGT, ALKP and ALB occurred between week 0 and week 24 (all $P$ values $>0.05$). INR showed a small but statistically significant decrease from week 0 (median value: 1.42) to week 24 (median value: 1.28, $P = 0.021$). TBIL did not show any significant change from week 0 to week 24. Conversely, UBIL showed a small but statistically significant increase at week 24 compared with baseline value (from 1.15 to 1.32 mg/dL, $P = 0.047$).

Median Child–Pugh, APRI, MELD and MDRD scores were not significantly changed in the follow-up period (all $P$ values $>0.05$, data not shown). Eight clinical episodes of decompensated liver cirrhosis occurred in the study period: ascites ($n = 5$), variceal haemorrhages ($n = 2$) and hepatic encephalopathy (one case).

## Discussion

Toxicity and resistance issues limit therapeutic choices in HIV-infected patients with advanced liver disease. Currently available data on the use of atazanavir in patients with liver disease include a clinical series of subjects with moderate/severe hepatic impairment, evaluated after they received a single dose of atazanavir 400 mg once daily.[31] In a clinical comparative study of atazanavir versus nelfinavir,[32] no differences in virological response were observed, over a period of 48 weeks, in patients co-infected with HBV or HCV compared with subjects with HIV infection alone. Bilirubin elevations were similar in the co-infected group. Pineda *et al.*[33] reported a low incidence of severe liver toxicity in 99 patients (60 of whom had chronic liver disease) receiving antiretroviral combinations including atazanavir. To our knowledge, the present study is the first to assess the potential benefits of $OLT_x$ and atazanavir efficacy, pharmacokinetics and safety in patients with ESLD.

No virological failures were documented in our study. A high number of liver decompensation episodes occurred during the follow-up period, confirming the clinical predominance of liver disease over HIV infection in the events observed during the study. Even when such episodes occurred, HAART was never interrupted for longer than 1 week. We believe that this capacity to maintain HAART was responsible for a statistically not significant, but clinically appreciable, increase of the CD4+ cell count between weeks 0 and 24. This amelioration in immune function was sufficient to maintain eligibility for $OLT_x$ in all the patients and to add three more subjects to the transplantation programme. In our study, an atazanavir-based regimen was effective to gain or maintain viral suppression and to preserve CD4+ cell count in all patients.

Median atazanavir AUC, $C_{trough}$ and $C_{max}$ were similar to those detected in other clinical trials in HIV-infected patients using atazanavir 400 mg once daily.[27,31,34] The median $C_{trough}$ value at all study weeks was well above the median wild-type 90% effective concentration of 14 ng/mL for atazanavir,[35] and also above the MEC suggested by BMS (100 ng/mL). These data, in conjunction with the lack of appreciable liver toxicity or severe increase in serum bilirubin levels, make atazanavir a useful drug option in patients suffering from ESLD. Our results demonstrated large inter-patient variability [with a percentage coefficient of variation (CV%) of AUCs equal to 76%] in subjects with ESLD, confirming the statement that hepatopathic individuals are candidates for TDM.[23] Nonetheless, no correlation was found between the degree of liver insufficiency and the patient-to-patient variation in atazanavir pharmacokinetics. Tenofovir was previously suggested to affect unboosted atazanavir exposure. With regard to atazanavir/tenofovir co-administration,[27,31,36] our data suggest the possibility of achieving adequate levels even without adding ritonavir, as shown by median plasma atazanavir $C_{trough}$ levels above the MEC among the eight subjects undergoing tenofovir-based nucleoside backbone therapy. PPIs are well known to interfere with atazanavir pharmacokinetics, with reduced or inadequate atazanavir absorption in the presence of the non-acid environment produced by these drugs.[27,37–39] Our data showed, within a context of great variability in atazanavir $C_{trough}$ levels, the presence of median values above the MEC in most patients in whom atazanavir was co-administered with PPIs.

During the study period, treatment with atazanavir did not worsen hepatic impairment or renal function. From baseline to week 24, UBIL increased significantly, but its absolute change was small in terms of clinical significance. Atazanavir is a known inhibitor of UGT1A1 and its use is associated with unconjugated hyperbilirubinaemia.[27] This observation indirectly suggests that the glucuronidation of atazanavir is not affected by liver disease, including cirrhosis.

The major methodological limitation of this study was the absence of a control group and the small sample size. In this particular setting, randomized trials are complicated and it may be difficult to achieve a large case series. Sample size constraints did not allow us to define the independent role of multiple cofactors potentially affecting atazanavir $C_{trough}$ levels in multivariate analyses, or to build a nomogram for dose adjustments according to the severity of liver failure.

TDM in subjects with liver impairment may be particularly useful to manage inter-patient variability and drug interactions, in the perspective of an optimal individualization of the antiretroviral regimen.

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## Transparency declarations

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