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# Incidence of Hyperbilirubinemia and Jaundice Due to Atazanavir in a Cohort of Hispanic Patients

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EDITOR: Hyperbilirubinemia is the most frequently described adverse affect of atazanavir (ATV). ATV is a competitive inhibitor of the enzyme UGT1A1, and can thus create a reversible, dose-dependent increase predominantly of unconjugated bilirubin.[1] In previous studies, the incidence of Grade III [> 2.5 times the upper limit of normality (ULN) according to the AIDS Clinical Trials Group definition] and Grade IV (>5 times ULN) hyperbilirubinemia ranged from <20% to 52%.[2–7] In the largest study, involving 2,404 patients in Italy, 44.6% of patients had Grade III or higher, and 7.2% had Grade IV hyperbilirubinemia.

According to this study, several factors increased the risk of hyperbilirubinemia during ATV therapy: elevated basal bilirubin, higher basal CD4 cell counts, and concurrent use of ritonavir booster.[7] In a multicenter study of 400 patients, concurrent use of ritonavir also increased the incidence of Grade III/IV hyperbilirubinemia: 59% among patients receiving ATV/r compared to 20% of patients receiving ATV.[8] Overall, the incidence of clinical jaundice in patients receiving ATV in dosages currently used in clinical practice has been reported as being 7–11%.[9,10] In multiple studies, hyperbilirubinemia and jaundice led to discontinuation of therapy for a small subset (1%) of patients.[8,9,11] There were no reported instances of permanent liver damage but jaundice may be cosmetically unacceptable. The aim of this study was to determine the prevalence of Grade III (or higher) hyperbilirubinemia and of clinical jaundice in a cohort of Hispanic patients receiving ATV. We also tried to determine the consequences of the mentioned adverse event on this population, and to determine if it is associated with liver damage.

We performed a retrospective review of medical records from patients attending three infectious diseases centers in Buenos Aires, Argentina (two private practices and a public hospital), who were at that time or previously on an antiretroviral regimen that included ATV (with or without ritonavir), regardless of antiretroviral backbone or the number of previous treatment failures. Patients who were identified as not being Hispanic were excluded. The values of total and indirect bilirubin were retrieved for the period in which ATV was taken. Highest values and times of occurrence were recorded. The following variables were analyzed: demographic variables, time to bilirubin (total and indirect) highest values, use of ritonavir, CD4 cell count at ATV initiation, liver aminotransferases, and hepatitis B and C virus (HBV and HCV) coinfection.

Descriptive results of continuous variables were expressed as mean and standard deviation (SD) values, or median and interquartile range (IQR) values, according to data distribution (parametric or nonparametric, respectively). Continuous variables were compared with parametric (Student's *t*) or nonparametric (Mann–Whitney *U*) tests, as required. Proportions were compared using the chi-square test, with Yates or Fisher corrections if needed.

The study population consisted of 108 Hispanic patients. The mean age was 43.4 years (SD: 8.34); 79% were male and 87% received ritonavir as booster. Risk factors for HIV acquisition were intravenous drug use (20%), men who have sex with men (32%), and heterosexual (48%).

The total follow-up was 121.7 patient-years. The median time of follow-up was 12 months (IQR: 6–18). The prevalence of HCV coinfection was 20% and of chronic HBV coinfection was 6%. The median CD4 count before starting ATV was 369 cells/mm$^3$ (IQR: 182–601).

The mean total bilirubin value before ATV was 0.58 mg/dl (SD: 0.27). After starting ATV, the mean highest total bilirubin value reached 3.27 mg/dl (SD: 1.83) and the mean highest indirect bilirubin value reached 2.76 mg/dl (SD: 1.70). The median time to reach the highest bilirubin values was 6 months (IQR: 3–12). Ninety percent of the patients had total bilirubin higher than normal at any time.

The percentage of patients with hyperbilirubinemia Grade III or higher was 63.6%. Those patients with values of bilirubin in ranges corresponding to Grade IV were 13.1%.

The percentage of patients with indirect bilirubin Grade III or higher was 77.8%. Clinical jaundice (ranging from scleral icterus to severe jaundice) was diagnosed by the physician in 22% of patients. More than 80% of these patients had scleral icterus only (mild jaundice).

There was no difference in the highest values of bilirubin between the patients who were and those who were not on ritonavir. There was no difference either between patients who started ATV with CD4 counts higher or lower than 200/mm$^3$, coinfection with HBV or HCV, sex, or age (Table 1).

No patient had liver aminotransferases values ≥3 times UNL. In addition, there was no relationship between the values of the aminotransferases and the values of bilirubin.

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Table 1. Mean Highest Total Bilirubin Values According to Different Variables and Odds Ratios for Developing Grade III or Higher Hyperbilirubinemia

| *Variable* | n | *Mean (SD) total bilirubin (mg/dl)* | p *(for inequality of means, ANOVA)* | *OR for bilirubin ≥ Grade III* | *OR confidence interval* | p |
|---|---|---|---|---|---|---|
| Sex | | | | | | |
| Female | 23 | 3.41 (2.18) | 0.69 | 1.02 | 0.36–2.90 | 0.97 |
| Male | 84 | 3.23 (1.74) | | | | |
| Age | | | | | | |
| <50 years | 86 | 3.19 (1.81) | 0.36 | 2.09 | 0.70–6.24 | 0.18 |
| >50 years | 21 | 3.60 (1.91) | | | | |
| CD4 | | | | | | |
| >200 | 66 | 3.22 (2.00) | 0.55 | 0.87 | 0.35–2.12 | 0.76 |
| <200 | 28 | 2.97 (1.49) | | | | |
| Ritonavir | | | | | | |
| No | 14 | 3.18 (2.39) | 0.85 | 1.34 | 0-42–4.20 | 0.62 |
| Yes | 92 | 3.28 (1.75) | | | | |
| HCV | | | | | | |
| No | 75 | 3.21 (1.79) | 0.73 | 1.02 | 0.36–2.90 | 0.97 |
| Yes | 19 | 3.37 (2.21) | | | | |
| HBV | | | | | | |
| No | 88 | 3.22 (1.9) | 0.93 | 3.15 | 0.35–28.11 | 0.28 |
| Yes | 6 | 3.30 (1.7) | | | | |

HCV, hepatitis C virus; HBV, hepatitis B virus.

None of the patients discontinued ATV due to hyperbilirubinemia or clinical jaundice.

In this cohort, the increase in bilirubin values caused by ATV seems to be higher than reported in previous studies performed in other populations. It is worth noting that even when bilirubin values were equal or higher than Grade III, or even when jaundice was noted, none of the patients chose to stop ATV. Confirming results from previous studies, it seems that hyperbilirubinemia is not associated with liver damage or with the presence of chronic viral hepatitis; in addition, it seems to be a benign hepatic side effect.

This study has several limitations. The observational and retrospective design makes it difficult to exclude biases. In addition, the number of patients included is relatively low and thus the power of the findings is smaller. We did not analyze hyperbilirubinemia or jaundice incidence in the subset of patients on tenofovir, which has been shown to decrease ATV levels, since less than 10% of the included population was receiving that drug. Tenofovir-containing regimens are now preferred and might be associated with a lower incidence of ATV-associated hyperbilirubinemia or jaundice. New studies are needed to assess this issue.

It has been shown that the risk of severe hyperbilirubinemia increases in the presence of the some UGT polymorphism, for example, the UGT1A1-TA7 allele[12,13] as well as by the 3435CrT polymorphism of MDR-1.[14] We did not test our patients for that, but higher frequencies of certain polymorphisms could explain the higher incidence of hyperbilirubinemia in our cohort. Future studies are needed to try to determine the prevalence and impact of these and/or other polymorphisms on bilirubin levels in Hispanic patients receiving ATV.

It is also of note that very few patients found the clinical jaundice bothersome, but still preferred to continue on ATV. We consider that it remains important to advise the patients who are about to start ATV about the occurrence of hyperbilirubinemia and jaundice, and reassure them since it has not been associated with liver damage, is only of cosmetic importance, and might be improved with certain measures.

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## Author Disclosure Statement

No competing financial interests exist.

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