Incidence of atazanavir-associated adverse drug reactions in second-line drugs treated south Indian HIV-1 infected patients

Dhakshinamoorthy Subashini1, Thongadi Ramesh Dinesha1, Jayaseelan Boobalan1, Lawrence Christopher Samuel1, Selvamuthu Poongulali1, Ambrose Pradeep1, Sunil Suhas Solomon1,2, Suniti Solomon1, Pachamuthu Balakrishnan1, Shanmugam Saravanan1

Abstract:
Background: Ritonavir-boosted atazanavir (ATV/r) is the preferred second-line protease inhibitor (PI) option for HIV patients in resource-limited settings; its pattern of adverse drug reactions (ADRs) has not been much reported from India; hence, in this study, we have analyzed the incidence of ATV/r-associated ADRs in Southern Indian HIV-1-infected patients.

Methods: In this prospective study, 111 HIV patients treated with ATV/r were included with at least 2 years follow-up visits for the emergence of hyperbilirubinemia, hypertransaminasemia, and serum creatinine elevation. The causality assessment was done based on the WHO scale for the causality assessment of suspected ADR.

Results: The incidence of severe hyperbilirubinemia, hypertransaminasemia, and creatinine elevation was 28.6, 0.76, and 1.62 cases/100 person years, respectively. 3TC/FTC + TDF (odds ratio [OR]: 6.07, confidence interval [CI]: 1.31–27.98, P = 0.015) nucleos (t) ide reverse transcriptase inhibitor backbone and male sex (OR: 18.64, CI: 2.13–162.93, P = 0.0082) were found to be significantly associated with hypertransaminasemia and creatinine elevation, respectively. The causality assessment of ADR was “possible” for all the participants. Kaplan–Meier analysis showed hyperbilirubinemia to emerge earlier (mean duration: 32.18 months, CI: 24.9–39.4 months) followed by hypertransaminasemia and creatinine elevation. Hyperbilirubinemia is an expected side effect associated with ATV/r which is benign, transient, and does not predispose to hypertransaminasemia.

Conclusion: Our study results show that patients starting ATV/r should be counseled for a good adherence in spite of the emergence of hyperbilirubinemia which generally reverts to normal range.

Key words: Adverse drug reaction, atazanavir, creatinine, hyperbilirubinemia, liver
hyperbilirubinemia in patients receiving ATV/r is distributed at a high frequency in Indians (35%) than the rest of the Asians.\[46\] In view of these facts and owing to the increased access to second-line antiretroviral therapy (ART) in India, and as there are not many reports from India pertaining to ATV/r related ADRs, in the current study we intend to analyze ATV/r associated ADRs among the HIV-1 infected patients of south India.

**Methods**

In this prospective analysis, the laboratory data of 111 HIV patients treated with ATV/r were included and the data of biochemical parameters (bilirubin, creatinine and alanine aminotransferase [ALT], aspartate aminotransferase [AST]) performed every 3 months and CD4 count measurement every 3–6 months were included, but routine viral load monitoring was not the standard of care. The Ethics Committee approval was obtained from the Institutional Review Board of YRG CARE, Chennai, India. The patients were followed to track hyperbilirubinemia, hypertransaminasemia, and serum creatinine elevation. The patients with baseline abnormality were removed from the analysis of respective group, based on that 13, 8, and 6 patients from bilirubin, transaminase, and creatinine groups, respectively were removed. Demographics of all patients were recorded as median (interquartile range [IQR]) for continuous variables and as numbers (percentage) for categorical variables. Adverse events were classified into Grade 1, 2, 3, and 4 according to the AIDS Clinical Trials Group classification; Grade 3 and 4 were considered severe.\[43\] The characteristics such as age, sex, baseline CD4 and its percentage, CD4 count at the time of ADR and its percentage, nucleos (t) ide reverse transcriptase inhibitor (NRTI) backbone, time since HIV positivity, time since ART initiation, time since ATV/r initiation, hemoglobin, and hypertension were considered as risk factors, and univariate and odds ratio (OR, Fischer’s exact test) were applied to find association. The causality assessment was done for them based on the WHO scale for the causality assessment of suspected ADR.\[41\]

**Results**

A total of 111 ART-experienced patients initiating ATV/r as the standard of care, majority being male (78.38%), with the median age of 36 years (IQR: 30.5–41.5) were followed longitudinally for a median duration of 38.96 months (IQR: 28.91–50.83 months) to observe the emergence of hyperbilirubinemia, hypertransaminasemia, and creatinine elevation. Ninety four (84.6%) were on NRTI back bone of lamivudine (3TC)/emtricitabine (FTC)+tenofovir (TDF), and 10(9%) on 3TC+azidothymidine (AZT) on 3TC+ abacavir (ABC), 2 (1.8%) on 3TC+ stavudine (d4T), and 1 (0.9%) each on 3TC+ didanosine (ddI) and Raltegravir.

On excluding patients with baseline abnormalities, the incidence rate of severe (Grade 3 or 4) unconjugated bilirubinemia was 28.6 cases/100 person years which was found in 64 (65.30%) patients. Moreover, 20 (31.25%), 21 (32.81%), and 23 (35.94%) developed hyperbilirubinemia during 1st, 2nd, and ≥3 years, respectively. However, Grade 1 and 2 hyperbilirubinemia was observed in 7 (7.14%) patients each. On the contrary, severe hypertransaminasemia was observed in only 3 (2.91%) individuals, with the lower incidence rate of 0.76 cases/100 person years. However, Grade 1 and 2 ALT/AST elevation was observed among 18 (17.48%) and 14 (13.33%) individuals, respectively. Creatinine elevation (Grade 3 and 4) was documented only in 6 (5.71%) patients with an incidence rate of 1.62 cases/100 person years; however, Grade 1 and 2 creatinine level was observed in 14 (13.3%) and 12 (11.43%) individuals, respectively [Table 1].

### Table 1: Demographic and clinical characteristics of the participants at study entry

| Characteristics | Total study participants (n=111) | Bilirubin (n=98) | ALT/AST (n=103) | Creatinine (n=105) |
|-----------------|---------------------------------|-----------------|-----------------|-------------------|
| Age             | 36 (30.5-41.5)                 | 38 (33-45)      | 38 (33-45)      | 38 (33-45)        |
| Sex (Male) [n (%)] | 87 (78.38%)               | 77 (78.57%)      | 78 (75.73%)      | 80 (76.19%)       |
| Mode of transmission |                       |                  |                  |                   |
| Heterosexual    | 96 (86.5%)                     | 84 (85.71%)      | 89 (84.76%)      | 90 (85.71%)       |
| Homosexual      | 2 (1.8%)                       | 2 (2.04%)        | 2 (1.90%)        | 2 (1.90%)         |
| Blood           | 8 (7.2%)                       | 7 (7.14%)        | 8 (7.62%)        | 8 (7.62%)         |
| Bisexual        | 1 (0.9%)                       | 1 (1.02%)        | 1 (0.95%)        | 1 (0.95%)         |
| Others          | 4 (3.6%)                       | 4 (4.08%)        | 3 (2.86%)        | 4 (3.81%)         |
| Baseline CD4(cells/µL) | 194 (65-295)            | 217 (87.5-294.5) | 181 (61-298)      | 219 (88-326)      |
| Baseline CD4%   | 12 (8-18)                      | 12 (8-17.25)     | 13 (8-18.25)     | 12 (8-19.5)       |
| CD4 (cells/µL)  | 302 (184-488)                  | 333 (200-423)    | 302 (181-486)    | 335 (196.5-500)   |
| CD4%            | 16 (11.2-20)                   | 14.5 (11.1-19.75) | 15 (12-20)       | 15 (11-19.75)     |
| Hemoglobin (g/dL) | 13.5 (10.6-15)               | 13.6 (11.1-14.9) | 13.1 (10.9-15)   | 13.4 (10.1-14.75) |
| Time since HIV positive (months) | 91.2 (53-138)          | 89.8 (52.4-136.9) | 92.46 (57.42-139.8) | 88.9 (53.23-139.7) |
| Time since ATV/r based regimen (months) | 23 (11-34)             | 19.95 (11.09-28.45) | 24.83 (11.15-37.36) | 18.3 (10.03-18.3) |
| Unconjugated Bilirubin (mg/dL) | -                      | 2.25 (0.9-3.6) | - | - |
| Serum ALT (IU/L) | -                      | - | 32 (19-71) | - |
| Serum AST (IU/L) | -                      | - | 58 (23.25-145.8) | - |
| Serum Creatinine (mg/dL) | -                      | - | 1.1 (0.9-1.3) | - |
| Estimated Glomerular filtration rate | -                      | - | 76.64 (62.23-87.69) | - |

Values are median [IQR] unless otherwise stated.
3TC/FTC+TDF backbone was found to be significantly associated with mild to greater transaminase elevation (OR: 6.07, confidence interval [CI]: 1.31–27.98, P = 0.015) although severe transaminasemia is found to be lower. On the other hand, creatinine elevation was slightly associated with age (OR: 1.0004, CI: 0.9997–1.0010, P = 0.035) and strongly associated with male gender (OR: 18.64, CI: 2.13–162.93, P = 0.0082). However, we did not find any association between hemoglobin level or hypertension with creatinine elevation [Table 1].

According to the WHO scale for the causality assessment of suspected ADR, all were classified as “possible.” On performing Kaplan–Meier analysis to estimate the time to the development of hyperbilirubinemia, hypertransaminasemia, and creatinine elevation, we found hyperbilirubinemia developed earlier (mean duration: 32.18 months, CI: 24.9–39.4 months), followed by hypertransaminasemia (81.128 months, CI: 73.6–88.6 months), then creatinine elevation (93.70 months, CI: 24.9–39.4 months), P < 0.0001 (log-rank test) [Figure 1]. On longer follow-up to identify the outcome of ADR, 50 (78.12%) with hyperbilirubinemia returned to normal, thus giving no scope for ATV/r substitution; however, for the rest, follow-up is needed as hyperbilirubinemia was observed only in their last follow-up.

**Discussion**

ATV/r being the only preferred second-line PI for children/adults,[1] its ADR is not much reported from India. Hence, in this prospective study, we analyzed 111 HIV-1-infected patients in southern India, initiating ATV/r for the emergence of hyperbilirubinemia, hypertransaminasemia, and creatinine elevation. Hyperbilirubinemia is an expected consequence of ATV/r as it is known to increase bilirubin via inhibition of UGT1A1; the proportion (65.30%) is quite high from the previous reports of 40–49%[7] which could be attributed to the higher frequency (35%) of UGT1A1 *28 allele among Indians.[4] To strengthen this, there was no association between bilirubin and hemoglobin levels, which signifies the fact that hyperbilirubinemia is independent of hemolysis. This finding of a lower proportion of hypertransaminasemia (2.91%) and lack of association with hyperbilirubinemia corroborates the previous reports of hyperbilirubinemia with the absence of overt liver injury among patients on ATV/r.[8,9] Moreover, the low incidence (5.71%) of Grade 3 and 4 creatinine elevation documented is in line with the low frequency of ATV/r-mediated kidney complications.[10,11] Although the previous studies have demonstrated a significant association between hyperbilirubinemia and ATV/r and abnormal baseline bilirubin level,[8] since we excluded patients with baseline hyperbilirubinemia and all patients were administered with ATV/r, we were unable to find an association with any of the variables.

Thus, from this present study, although we found a higher proportion of ATV/r-associated hyperbilirubinemia among South Indians, it is not found to be associated with liver injury, and moreover, it reverts to normalcy. This affirms the safety of ATV/r, and hence, the patients advised for ATV/r must be counseled for a good adherence despite icterus, which has otherwise some cosmetic concern that disappears eventually.

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**Conflicts of Interest**

There are no conflicts of interest.

**References**

1. National Guidelines on Second-Line and Alternative First-line ART for Adults and Adolescents; May, 2013. Available from: http://www.naco.gov.in/upload/Policy%20and%20Guidelines/Antiretroviral%20Therapy%20for%20HIV-Infected%20Adults%20and%20Adolescents.pdf. [Last accessed on 2014 Dec 23].

2. Havlir DV, O’Marro SD. Atazanavir: New option for treatment of HIV infection. Clin Infect Dis 2004;38:1599-604.

3. Choi H, Jeong SJ, Lee HS, Chin BS, Choi SH, Han SH, et al. Two cases of multidrug-resistant human immunodeficiency virus infection treated with atazanavir and lopinavir/ritonavir combination therapy. J Korean Med Sci 2008;23:737-9.

4. Choe PG, Park WB, Song JS, Kim NH, Song KH, Park SW, et al. Incidence of atazanavir-associated hyperbilirubinemia in Korean HIV patients: 30 months follow-up results in a population with low UDP-glucuronosyltransferase1A1*28 allele frequency. J Korean Med Sci 2010;25:1427-30.

5. AIDS Clinical Trials Group. Table for Grading Severity of Adult Adverse Experiences. Rockville, MD: Division of AIDS, National Institute of Allergy and Infectious Diseases; 1992.

6. The Use of the WHO-UMC System for Standardised Case Causality Assessment. Available from: http://www.who-umc.org. [Last accessed on 2014 Feb 28].

7. Johnson M, Grinsztejn B, Rodriguez C, Coco J, DeJesus E, Lazzarin A, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS 2005;19:153-62.

8. Torti C, Lapadula G, Antinori A, Quirino T, Maserati R, Castelnuovo F, et al. Hyperbilirubinemia during atazanavir treatment in 2,404 patients in the Italian atazanavir expanded
access program and Master Cohorts. Infection 2009;37:244-9.

9. Sanne I, Piliero P, Squires K, Thiry A, Schnittman S; AI-Clinical Trial Group. Results of a phase 2 clinical trial at 48 weeks (AI424-007): A dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. J Acquir Immune Defic Syndr 2003;32:18-29.

10. Chan-Tack KM, Truffa MM, Struble KA, Birnkrant DB. Atazanavir-associated nephrolithiasis: Cases from the US Food and Drug Administration’s Adverse Event Reporting System. AIDS 2007;21:1215-8.

11. Couzigou C, Daudon M, Meynard JL, Borsa-Lebas F, Higuero D, Escaut L, et al. Urolithiasis in HIV-positive patients treated with atazanavir. Clin Infect Dis 2007;45:e105-8.