

RESEARCH ARTICLE

Evaluation of adverse drug reaction profile of antiretrovirals in HIV-positive patients in a tertiary care hospital

Chaithanya Malalur¹, Smita Shenoy¹, Muralidhar Varma², Asha Kamath³, Hasitha Manohar¹, Kavitha Saravu²

¹Department of Pharmacology, Kasturba Medical College, Manipal University, Manipal, Karnataka, India, ²Department of Medicine, Kasturba Medical College, Manipal University, Manipal, Karnataka, India, ³Department of Community Medicine, Kasturba Medical College, Manipal University, Manipal, Karnataka, India

Correspondence to: Smita Shenoy, E-mail: smita.shenoy@manipal.edu

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ABSTRACT


Background: Adverse drug reactions (ADRs) to antiretrovirals have been a matter of concern as they can affect patient compliance and treatment outcome. Hence, it is important to detect them early and institute appropriate treatment. **Aims and Objective:** To assess the prevalence, distribution, causality, severity, predictability and preventability of ADRs to antiretrovirals and to identify risk factors for their development in a tertiary care hospital in South India. **Materials and Methods:** This was a descriptive observational study. Data were collected from the case records of adult, treatment naïve HIV-positive patients, newly initiated on antiretroviral drugs, January 2012 onward and closure of data set was on 31st December 2014. **Results:** A total of 238 cases met the inclusion criteria. Overall, 56 ADRs were noted. ADRs were observed in 39 males and 17 females. They were common in the age group 51-60 years. Anemia was the most common ADR followed by rash and hyperpigmentation. Most of the ADRs observed were of mild severity, requiring neither change in regimen nor any specific treatment. Zidovudine caused the highest number of ADRs, followed by nevirapine and stavudine. Most ADRs occurred within 6 months of starting antiretroviral therapy (ART). Causality relationship between drug and ADR was graded as “possible” according to WHO causality assessment scale. No statistically significant correlation of age, gender, weight, hemoglobin, CD4 count and the presence of opportunistic infections to the development of ADRs were noted. **Conclusion:** Regular monitoring, an early detection of ADRs to antiretrovirals and their treatment is essential to optimize ART.

KEY WORDS: Pharmacovigilance; Antiretroviral Therapy; Zidovudine; Tenofovir

INTRODUCTION

Antiretroviral therapy (ART) is associated with a wide range of adverse drug reactions (ADRs), varying from mild

intolerance to life-threatening side effects. The short-term (occurring within few weeks of ART initiation) adverse effects include nausea, vomiting, diarrhea, rash, hypersensitivity reactions, urticarial reaction, erythema multiforme, toxic epidermal necrolysis or Stevens–Johnson syndrome, hepatotoxicity, drowsiness, dizziness, confusion, and vivid dreams. Intermediate (occurring within the first few months of start of ART) adverse effects are anemia, neutropenia, bone marrow suppression, hyperpigmentation of skin, nails and mucous membranes, lactic acidosis, peripheral neuropathy, and pancreatitis. Long term (within 6-18 months of ART initiation) adverse effects include lipodystrophy, lipoatrophy,

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dyslipidemia, diabetes, abnormalities in skin, nail, and hair.^[1] The prevalence of ADRs to antiretrovirals in a previous study done in 2013 in India and was found to be 31%.^[2]

These ADRs lead to modification or change in ART regimen, increase in morbidity and mortality, poor quality of life as well as compliance to therapy. The latter could result in failure of ART and development of resistance while increasing the economic burden on the patient and society.^[3] Hence, it is important to detect ADRs early, treat them, identify the suspect drug and risk factors for ADRs for better management of patients.

Objectives

1. To assess the prevalence, distribution, causality, severity, predictability and preventability of ADRs to antiretrovirals
2. To identify risk factors for the development of these ADRs.

MATERIALS AND METHODS

The study was conducted after obtaining clearance from the Institutional Ethics Committee, Kasturba Hospital, Manipal. The patient data collected was anonymized. The study was a descriptive observational study. The study site was HIV clinic, Kasturba Hospital, Manipal. Data were collected from outpatient and inpatient case records of HIV-positive patients above 18 years of age, newly initiated on ART, January 2012 onward. Closure of data set was on 31st December 2014.

The ADRs were noted in “suspected ADR reporting form” of Central Drugs Standard Control Organization. Causality was assessed using WHO-UMC standardized case causality assessment,^[4] severity by Hartwig severity scale,^[5] predictability using Council for International Organizations of Medical Sciences (CIOMS) criteria^[5,6] and preventability by Schumock and Thornton criteria.^[5]

Statistical Analysis

All statistical tests were done using SPSS Version 16. Descriptive statistics was used to describe ADR pattern. Pearson’s Chi-square test was used to find differences between groups with $P < 0.05$ considered as significant. Kaplan-Meier curves were used to compare “time-to-event” between groups and Breslow test was used to test for significance.^[7] Logistic regression was used to ascertain effects of age, gender, CD4 on the development of an ADR to antiretrovirals.

RESULTS

A total of 238 HIV-positive patients met the inclusion criteria. Of these, 179 were male (75.2%) and 59 were female (24.8%).

There was a total of 56 ADRs to antiretrovirals, which amounts to a prevalence rate of 23.5%. Among the patients who developed ADRs, 39 patients were male (69.6%) and 17 were female (30.4%). Overall, the median age of the patients was 43 years, ranging from 28 to 72 years. ADRs were most common (30.4%) in the age group 51-60 years (Table 1).

Out of the 56 ADRs to ARVs noted, the most common reaction was anemia accounting up to 27.23%. Drug-induced rash was the second most common (23.63%) ADR noted, followed by hyperpigmentation and lipodystrophy (9.09% each). The numbers and description of different types of ADRs caused by antiretroviral drugs are detailed in Figure 1.

The median time taken for onset of ADRs was analyzed. Nausea and vomiting was found to have the shortest latency (median: 11 days) for occurrence, from the date of starting of ART, whereas drug-induced pancreatitis had the maximum latency period (median: 285 days) for onset, from the date of starting of the ART. For all other drugs, the timeline for occurrence for ADRs from the date of initiation of ART is shown in Figure 2.

The frequency of ADRs was compared against baseline CD4 values of the patients to assess for any patterns. Patients were classified into three groups based on their baseline CD4 values as follows: CD4 count <100 cells/mm³, CD4 count between 101 and 200 cells/mm³, and CD4 count more than 200 cells/mm³. The frequency of ADRs for different baseline CD4 levels is shown in Table 2.

To identify patient associated risk factors for developing ADR, factors such as age, gender, body weight, hemoglobin,

Table 1: Frequency of ADRs in each age group

Age group (in years)	Number of patients (n=238)	Patients with ADR (n=56)	Percentage patients with ADR
<30	15	2	13.3
31-40	80	17	21.2
41-50	105	26	24.8
51-60	23	7	30.4
>60	15	4	26.7

ADRs: Adverse drug reactions

Table 2: Distribution of ADRs across patients’ baseline CD4 range

Baseline CD-4 (cells/mm ³)	Number of patients	Patients with ADRs	Percentage
<100	132	32	24.2
100-200	71	14	19.7
>200	35	10	28.6

ADRs: Adverse drug reactions

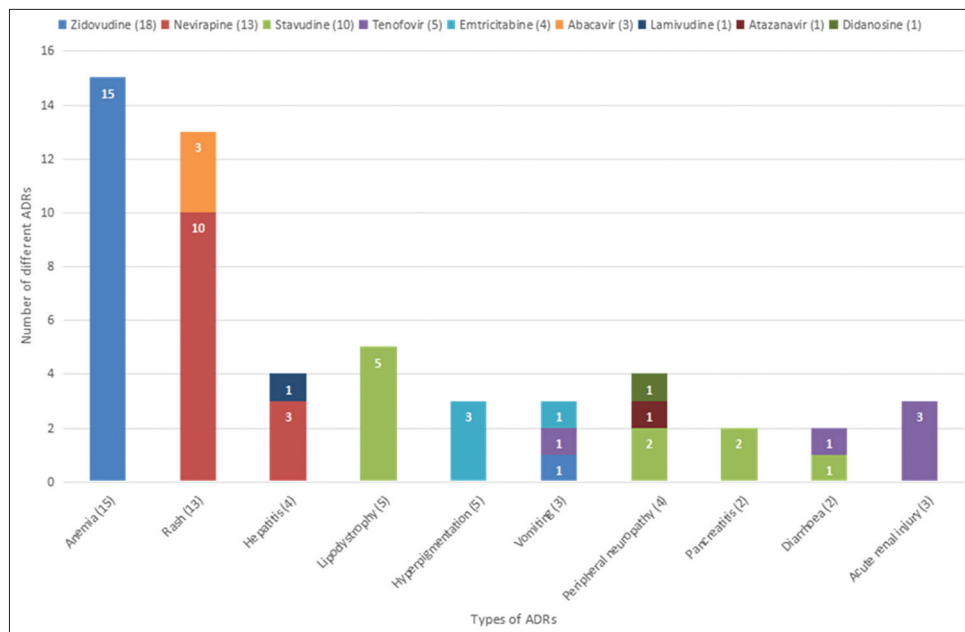


Figure 1: Frequency of adverse drug reactions caused by antiretroviral drugs

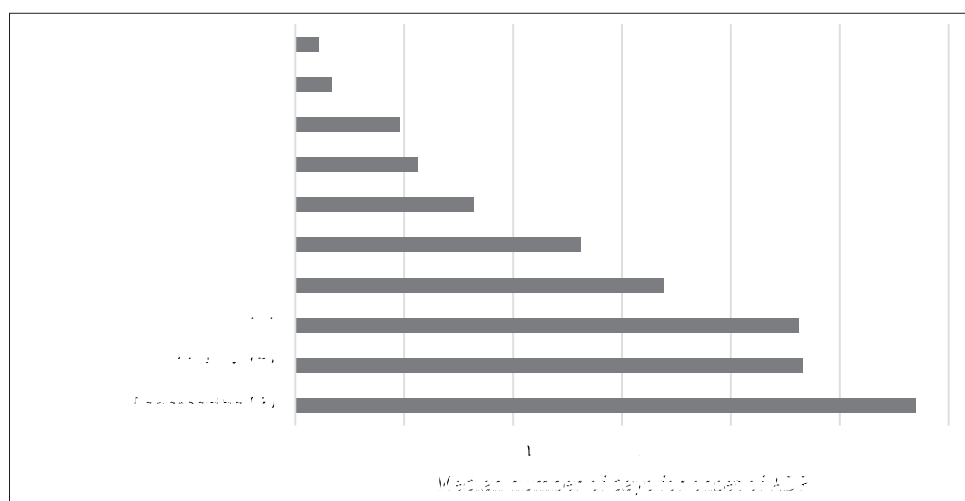


Figure 2: Median time taken for onset of adverse drug reactions from the date of initiation of antiretroviral therapy (n=56)

and CD4 count were assessed using Kaplan-Meier curves comparing time to event (occurrence of ADR) from time of starting ART and Breslow (generalized Wilcoxon) test was used to determine if there were differences in the time-to-event distribution for the different groups. However, none of the parameters assessed yielded a statistically significant correlation ($P = 0.786$ for age; $P = 0.275$ for gender; $P = 0.702$ for weight; $P = 0.796$ for hemoglobin; $P = 0.215$ for CD4 count) in identifying a risk factor.

A binomial logistic regression was performed to ascertain the effects of age, gender, presence or absence of OIs, baseline hemoglobin, weight and CD4 count on the likelihood that the patients will develop an ADR. The logistic regression model was not statistically significant in predicting likelihood

of developing ADR. However, the model explained 2.2% (Nagelkerke R^2) of the variance in the occurrence of ADR among the different groups and correctly classified 76.5% of cases. Increasing age and lower baseline CD4 count were associated with a slightly increased likelihood of developing an ADR. However, both of the observations noted were statistically not significant.

Outcomes of the ADRs noted were analyzed and the findings showed that 12 cases (21.43%) out of the 56 ADRs required a change of regimen, whereas the remaining 44 cases (78.57%) did not need any change in regimen. 18 out of 56 cases (32.14%) required a specific treatment for managing the ADR, whereas the other 38 (67.86%) did not need any treatment for the adverse reaction.

Causality Assessment

All the 56 ADRs observed belonged to the category of “possible” according to WHO causality assessment scale.^[4] Severity: According to Hartwig severity scale,^[5] out of 56 ADRs observed, 38 (67.85%) were “mild” (level 1 or 2), 16 (28.57%) were “moderate” (level 3, 4 or 5) and 2 (3.57%) were “severe” (level 6 or 7). Predictability: According to the criteria by the “CIOMS” guidelines,^[5,6] for preparing core clinical-safety information on drugs, all the 56 ADRs noted in the study were found to be predictable. No new or previously undocumented ADR to any of the drugs was observed. Preventability: 49 ADRs (87.5%) were found to be “not preventable” and only 7 ADRs (12.5%) were “probably preventable” as per modified Schumock and Thornton scale.^[5] Serious adverse events (SAE): There were 4 SAE observed in the study resulting in increased hospital stay by more than 1 day; however, no deaths occurred because of any ADR.

DISCUSSION

The most common regimen prescribed in the hospital here was zidovudine + lamivudine + nevirapine, which happens to be regimen I of National AIDS Control Organization (NACO) and is recommended as a first-line regimen.^[8] A previous study on ADRs in HIV patients in a tertiary care center in India by Srikanth *et al.*, had also shown zidovudine + lamivudine + nevirapine combination as the most commonly used antiretroviral regimen.

In this study, the prevalence of ADRs was 23.52% as compared to 50.63% in a study by Masenyetse *et al.*^[7] Since the present study was a case record based observational study, the ADRs were captured mainly based on clinician’s notes in the patient case files. This might be one of the reasons why the prevalence was relatively on a lower side.

Among the patients who developed an ADR, the majority were aged between 51 and 60 years. This trend of higher frequency of ADRs in elderly population may be related to the presence of comorbidities and its treatment, or the longer duration of disease (HIV) in them. However, the previous study by Srikanth *et al.*, had observed most of the patients were between age 31 and 40 years.^[9]

Serum hemoglobin levels were routinely measured to assess response to therapy. It also helps in early detection of drug-induced anemia. Hence, the most common ADR observed in this study was anemia followed by rash and these findings were consistent with observations in the previous study by Srikanth *et al.*^[9] In this study, zidovudine-induced adverse effects were mainly in the form of anemia, hyperpigmentation, and nausea/vomiting which was similar to findings from a previous study.^[10] The incidence of nevirapine-induced rash was similar to previously reported studies.^[11] Studies have shown the prevalence of 10-80% for stavudine-induced

lipodystrophy and 6-37% for peripheral neuropathy.^[12-14] This was high as compared to our study. The declining use of stavudine along with a shift to zidovudine/tenofovir-based regimen in our hospital could account for the difference in prevalence of ADRs.

There were 3 cases of tenofovir-induced acute kidney injury noted in our study, and similar incidence rates were reported in previous studies.^[15,16] Emtricitabine and abacavir were generally well tolerated and had few adverse reactions like hyperpigmentation of palms and soles, rash and diarrhea which correlated with findings in previous studies.^[17,18]

The average time taken for onset of an ADR from the time of initiation of ART was similar to the findings of NACO.^[8] While comparing the distribution of ADRs with the CD4 cell count, it was observed that majority of ADRs occurred in patients who had a CD4 cell count >200 cells/mm³. Similar findings were also observed in a study by Lartey *et al.*, where they found CD4 cell count >250 cells/mm³ was associated with more ADRs.^[19] Increased incidence of hypersensitivity to drugs in HIV patients can be explained by the fact that there is alteration in immune system function in HIV patients, leading to a predominant TH2 response. In addition, cytokines can affect cytochrome P-450 enzymes and drug metabolism which can possibly lead to drug toxicities.^[20]

Possible predictors/risk factors for the development of ADRs to ARVs include age, gender, weight, and hemoglobin. Elderly are more likely to be at risk of ADRs due to age-related changes in drug absorption, distribution, and elimination. In our study, patients <30 years of age had a lower incidence of ADR compared to those in older age groups. Gender differences in body size, fat, hepatic and renal functions can affect drug disposition.^[21] There have been reports of 2 to 11.7-fold increase in risk for developing toxicity to antiretrovirals in females.^[22] In our study, male patients had better survival in terms of not developing ADRs compared to females; however, in both these observations the association was not significant. This was similar to findings in the study by Masenyetse *et al.*^[8]

Many drugs bind to plasma proteins. The extent to which ARVs bind to plasma proteins is variable ranging from <5 to >99%.^[23] Low hemoglobin level in HIV-positive patients is generally associated with poor disease control and this may affect the incidence of ADRs.^[24] However, in this study, no correlation was found with regard to the occurrence of ADRs in relation to body weight and hemoglobin levels.

All the ADRs noted in the study were found to fall into category of “possible” in terms of causality assessment as per WHO causality scale.^[4] The reason why none of them could be considered as “certain” was probably because, in mild reactions dechallenge was not done and in few moderate or severe reactions, a satisfactory rechallenge test cannot be done.^[25,26]

ADRs can be classified as mild, moderate or severe according to Hartwig severity scale.^[5] This classification provides a uniform approach to management of ADRs. In this study, the majority of ADRs were mild requiring no treatment. However, in another study conducted in a tertiary care hospital in India by Srikanth *et al.*, the majority of the ADRs (58.5%) were of moderate severity.^[9]

In patients who have never received the drug previously, predictability is assessed based on the incidence of ADRs reported in product information or other literature. The incidence of <1/100 is considered as “not predictable” and an incidence rate of more than 1/100 is considered as “predictable.” Hence in this study, based on the incidence rates, all ADRs were predictable.^[5,6]

To identify causes of ADRs such as wrong dose or frequency, or failure to monitor the patient for expected early signs of drug toxicities and to assess if the ADR could be preventable or not, modified Schumock and Thornton preventability scale is employed.^[5] Based on this, in our study, most of the ADRs (87.5%) were found to be not preventable.

Limitations

The relatively small sample size affected the comparison of data with that obtained from other studies. Furthermore, probably because of the small sample size, evaluation for risk factors and predictors did not yield any statistically significant results.

CONCLUSION

Anemia was the most common ADR followed by rash and hyperpigmentation in our study. Most of the ADRs observed were of mild severity, requiring neither change in regimen nor any specific treatment. Zidovudine was implicated in the highest number of ADRs, followed by nevirapine and stavudine. The most ADRs occurred within 6 months (short term) of starting of ART. Age, gender, weight, hemoglobin, CD4 count, and presence of OIs were assessed as possible predictors/risk factors for developing an ADR to ARVs; however, no statistically significant correlation could be established.

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