National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Causality, severity and preventability assessment of adverse drug reactions in patients received anti-retroviral therapy in a tertiary care hospital: A retrospective study

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Received: August 04, 2016; **Accepted:** August 22, 2016

ABSTRACT

Background: The cornerstone of management of patients with human immunodeficiency virus/acquired immunodeficiency syndrome (AIDS) infection is highly active antiretroviral therapy (HAART). However, antiretroviral drugs are highly toxic and are associated with various adverse drug reactions (ADRs). Therefore, many patients require the withdrawal of the drug or even discontinue the treatment resulting in the treatment failure. **Aims and Objectives:** To study the demographic details and type of ADRs in patients receiving ART and to do causality, severity, and preventability assessment of the spontaneously reported ADRs. **Materials and Methods:** This was a retrospective cross-sectional observational study conducted for 18 months from January 2015 to June 2016 in Rajendra Institute of Medical Sciences, Ranchi. Spontaneously reported ADR data were evaluated for the patient demography, type of ADRs, drugs/regimes responsible, and body system affected. ADRs were assessed for their causality, severity, and preventability as per the standard scales. **Results:** Out of 356 patients given ART 197 ADR reports received which showed slight male predominance. 86.80% cases fell in 25-54 years age group with a mean age of 38.38 ± 10.74 years. The majority were neuropsychiatric (29.44%) and gastrointestinal-hepatobiliary (24.87%) followed by hematologic, dermatologic, and metabolic ADRs. Regimen containing tenofovir, lamivudine, and efavirenz were responsible for maximum number of ADRs (49.23%) followed by zidovudine, lamivudine, nevirapine (23.85%). 88.85% of ADRs were possible, 9.14% probable, and 2.03% certain according to the World health organization-Upsala monitoring centre causality assessment. 67.51% ADRs were mild followed by 29.44% moderate and 3.04% severe. 21.82% ADRs were definitely preventable, 37.06% probably preventable, and 41.12% not preventable. **Conclusion:** Although HAART is effective in decreasing AIDS-related deaths, it is associated with a number of ADRs. To maintain the patient compliance judicious use of ART and continuous monitoring of ADRs and their effective treatment prevention is advocated.

KEY WORDS: ART; ADR; World Health Organization-Upsala Monitoring Centre Causality Assessment; Causality; Severity; Preventability

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2017.7.0821922082016	

INTRODUCTION

An adverse drug reaction (ADR) has been defined by the WHO as "any unintended and noxious response to a drug which occurs at doses normally used in human beings for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."[1] World health

organization-Upsala monitoring centre (WHO-UMC), the two principal collaborating bodies started pharmacovigilance programme to keep a watch on various ADRs and events occurring worldwide. Lazarou et al.[2] through a meta-analysis of 39 epidemiological studies found that ADRs ranked between fourth and sixth leading causes of deaths in the USA. Realizing the significance of monitoring ADRs to improve public health, Pharmacovigilance Programme of India (PvPI) was started in 2010.[3] According to this program, ADR monitoring centers have been set up in many medical institutions all over the country to estimate the frequency of ADRs occurring with various drugs among the Indians.

National adult (15-49 years) human immunodeficiency virus (HIV) prevalence is estimated at 0.26% (0.22-0.32%) in 2015, whereas Jharkhand had prevalence below 0.20%, i.e., less than national level.[4] After initiation of treatment in April 2004 under NACP, acquired immunodeficiency syndrome (AIDS)-related deaths started to decline by 2007, falling by 54% from 2007 to 2015 against a global average of 41% decline during 2005-2015.[5] The cornerstone of management of patients with HIV/AIDS infection is highly active antiretroviral therapy (HAART).[6] However, Antiretroviral drugs are highly toxic and are associated with various ADRs. Therefore, many patients require the withdrawal of the drug or even discontinue the treatment resulting in treatment failure.[7] d'Arminio Monforte et al.[8] in a study found that those who discontinued therapy, 21% did so because of toxicity. Major toxicities commonly include bone marrow suppression, pancreatitis, hypersensitivity, hepatic necrosis, neuropsychiatric complaints, and nephrolithiasis.[9]

Spontaneous reporting of ADRs voluntarily by the health-care professionals has been the core data-generating system of pharmacovigilance for years. It plays a major role in identifying and reporting of any adverse events to the pharmacovigilance coordinating center, health/regulatory authority or to the drug manufacturer itself.[10]

The aim of this study was to evaluate the incidence of ADRs related to ART in an economically backward state of India, i.e., Jharkhand and to retrospectively assess the causality, severity, and preventability of ADR in AIDS patient.

MATERIALS AND METHODS

This was a retrospective study, which was carried out in the Department of Pharmacology, pharmacovigilance unit of Adverse Drug Monitoring Centre (AMC), RIMS, Ranchi. The causality was assessed with the help of Naranjo ADR probability scale,[11] and WHO-UMC causality categories.[12] Severity was assessed by Modified Hartwig and Siegel Scale.[13] Preventability was assessed by Modified Hartwig and Siegel Scale and Modified Schumock and Thornton Scale.[14]

Study Design

A retrospective cross-sectional study was conducted utilizing collection of spontaneously reported ADR data of HIV-1 infected person irrespective of age and sex, who received any of the ART drugs as part of their ART from January 2015 to June 2016. Discretion of information acquired was secured and all the measures to maintain confidentiality were undertaken, during the study. The ADRs reported to AMC were analyzed by pharmacovigilance team comprising pharmacologists and a pharmacovigilance associate working under PvPI.

Statistical Analysis Used

The study used descriptive statistics and the values were expressed in numbers, percentages, proportions, and mean wherever appropriate. Data were subdivided based on age, sex, drugs, and body systems/organs involved.

RESULTS

During the study period from January 2015 to June 2016, 356 patients were given ART. 197 ADR reports related to ART were received spontaneously which revealed a total of 267 different ADRs. Out of 197 cases, 104 (52.79%) were male whereas 93 (47.20%) were female (Table 1). The maximum number of cases, i.e., 171 (86.80%) fell between 25 and 54 years of age among which 79 (40.10%) were in age group 35-44 years (Table 1). The study group had a mean age of 38.38 ± 10.74 years. Tenofovir, lamivudine, efavirenz (TLE) combination ART was responsible for a maximum number of ADRs 97 (49.23%) followed by combined zidovudine, lamivudine, and nevirapine (ZLN) 47 (23.85%) (Table 2). Efavirenz was leading single drug responsible for 16 (8.12%) of total ADRs followed by zidovudine 13 (6.59%). Almost 30% of total ADRs were neuropsychiatric followed by almost 25% Gastro-entero and Hepatobiliary ADRs (Table 3). ADRs related to hematological, dermatological and metabolic systems separately averaged around 13.5%. Surprisingly, no respiratory ADR was reported. According to WHO-UMC causality assessment, most of the ADRs fell in the category of "possible" (88.85%) followed by "probable" (9.14%) and "certain" (2.03%) (Table 4). Similarly, analysis with Naranjo algorithm-ADR probability scale revealed that majority of the ADRs were possible (86.80%) followed by probable (9.64%) and definite (1.52%) (Table 5). This may be due to the differences in assessment methods of the scales, the former being subjective and the later more objective. Severity assessment using Modified Hartwig and Siegel's scale showed that maximum ADRs were mild 133(67.51%), followed by moderate 58 (29.44%) and Severe 6 (3.04%) (Table 6). Using Modified Schumock and Thornton preventability assessment scale 21.82% (43) ADRs were found to be definitely preventable whereas 37.06% (73) were probably preventable but 41.12% (81) were not preventable (Table 7).

Table 1: Distribution of demographic details

Characteristics	Number of ADRs (*n*=197) (%)	Mean age±SD
Age (years)		
≤14	7 (3.55)	9.71±3.41
15-24	7 (3.55)	21.28±2.05
25-34	55 (27.91)	31.23±2.15
35-44	79 (40.10)	39.20±3.11
45-54	37 (18.78)	49.43±2.90
55-64	10 (5.07)	57.70±2.32
≥65	2 (1.01)	70±5
Gender		
Male	104 (52.79)	
Female	93 (47.21)	

ADRs: Adverse drug reactions, SD: Standard deviation

Table 2: Drugs/regimens and their contribution to ADRs

Drugs/combination ART	*n*=197 (%) of ADRs
TLE	97 (49.23)
ZLN	47 (23.85)
Efavirenz	16 (8.12)
Zidovudine	13 (6.59)
TLAR	7 (3.55)
TLN	5 (2.53)
ZLE	5 (2.53)
SLN	1 (0.51)
SLE	1 (0.51)
Nevirapine	1 (0.51)
Lamivudine	1 (0.51)
Stavudine	1 (0.51)
Tenofovir	1 (0.51)
ALN	1 (0.51)

ADRs: Adverse drug reactions, ART: Antiretroviral therapy, TLE: Tenofovir, lamivudine, efavirenz, ZLN: Zidovudine, lamivudine, nevirapine, TLAR: Tenofovir, lamivudine, atazanavir, ritonavir, TLN: Tenofovir, lamivudine, nevirapine, ZLE: Zidovudine, lamivudine, efavirenz, SLN: Stavudine, lamivudine, nevirapine, SLE: Stavudine, lamivudine, efavirenz, ALN: Abacavir, lamivudine, nevirapine

Table 3: Body systems involved and their proportions

Body system involved	*n*=197 (%) of ADRs
Neuropsychiatric disorders	58 (29.44)
Gastrointestinal and hepatobiliary system	49 (24.87)
Hematological system	29 (14.72)
Dermatological system	27 (13.70)
Metabolic disorders	25 (12.69)
Urogenital system	12 (6.09)
Endocrine system	10 (5.07)
Musculoskeletal system	8 (4.06)
Cardiovascular system	5 (2.53)
Respiratory system	0 (0)
Others/general body functions	14 (7.10)

ADRs: Adverse drug reactions

Table 4: Causality assessment using WHO-UMC scale

Causality	*n* (%) of ADRs
Certain	4 (2.03)
Probable	18 (9.14)
Possible	175 (88.85)
Unlikely	0 (0)
Conditional/unclassified	0 (0)
Unassessable/unclassifiable	0 (0)

ADRs: Adverse drug reactions

Table 5: Causality assessment using Naranjo ADR probability scale

Causality	*n* (%) of ADRs
Definite	3 (1.52)
Probable	19 (9.64)
Possible	171 (86.80)
Doubtful	0 (0)

ADRs: Adverse drug reactions

DISCUSSION

In our study, the prevalence of ART-related ADR reported was 55.34%. This was much lower than that of 94% reported by Malangu[15] (2008) and 71.1% by Sharma et al.[16] but higher than Jha et al.[19] (16.21%). The average number of ADRs a patient was found to be 1.355. In a study by Nagpal et al.,[18] 90.6% cases were found to have ADRs including 618 episodes in various systems, the abdominal, and central nervous systems were the most affected.[18] Likewise, our study also had neuropsychiatric and abdominal ADRs as the first two most common (Table 3). Our study has shown a slightly higher prevalence in males compared to females (52.79% males and 47.21% females). This was comparable to that found by Jha et al. (53.5% males and 46.5% females)[19] but differed from that by Srikanth et al.,[17] i.e., higher in female population (41.82%) compared to males (33.05%). The most frequent and second most common ADR in our study was vertigo/dizziness (12.69%) and Anemia (11.67) whereas in a study by Singh et al.[20] in Chhattisgarh it was peripheral neuropathy (20.83%) and skin rash (15.83%), respectively. On the other hand, peripheral neuropathy, anemia, and nail hyperpigmentation were the most common side effects observed by Kumarasamy et al.[9] Out of all zidovudine-related ADRs incidence of anemia was found to be in 27.69% which is slightly higher as compared to Curkendall et al.[21] (24.3%) and Sharma et al.[16] (20%). Anemia was the reason for a maximum number of hospitalizations/prolongation of hospital stay in our study. Efavirenz is commonly associated with central nervous system side effects[22,23] also in our study maximum number of neuropsychiaric ADRs including

Table 6: Severity assessment using modified Hartwig and Siegel's scale

Severity of ADRs	*n* (%) of ADRs
Mild	133 (67.51)
Moderate	58 (29.44)
Severe	6 (3.04)

ADRs: Adverse drug reactions

Table 7: Preventability assessment using modified Schumock and Thornton scale

Preventability of ADRs	*n* (%) of ADRs
Definitely preventable	43 (21.82)
Probably preventable	73 (37.06)
Not preventable	81 (41.12)

ADRs: Adverse drug reactions

vestibular symptoms like vertigo/dizziness were attributed to efavirenz. Immune reconstitution inflammatory syndrome (IRIS) occurred in a 50-year-old patient on TLE combination ART that indicates co-existence of HIV-related opportunistic infection or disease.[24] tuberculosis-IRIS was observed in four cases by Sharma et al.[16] Lipodystrophy was observed in only 2.54% which was too low as compared with 20.04% of cases by Singh et al.[20] and 14.5% by Sharma et al.[16] Efavirenz-induced gynecomastia[23] was found in 4.06% of cases. Endocrine and metabolic disorders such as diabetes mellitus, hypothyroidism, and dyslipidemia were observed with lamivudine-based ART especially ZLN combination therapy (about 17.77% taken together). Renal toxicity was associated with tenofovir-based ART; one case of life-threatening renal failure was observed. Although various drugs caused skin and mucosal lesions, TLE combination ART was associated with maximum number of cases. Severe eczematous lesion was caused by abacavir regimen. Hepatotoxicity/deranged liver function was seen in 11.17% of reports especially lamivudine-based regime.

In our study, 88.85% of ADRs were possible, 9.14% probable and 2.03% were certain (WHO-UMC causality assessment) and 86.80% possible, 9.64% probable and 1.52% definite (Naranjo algorithm-ADR probability scale), respectively. Maximum ADRs were mild 133 (67.51%) followed by moderate 58 (29.44%) and severe 6 (3.04%). 43 (21.82%) ADRs were found to be definitely preventable whereas 73 (37.06%) were probably preventable, 81 (41.12%) were not preventable. Causality assessment done according to the Naranjo's scale by Jha et al. revealed that 66.04% AEs were "probable" and 33.96% were "possible," whereas by Nagpal et al. 6.63% ADRs were probable and 93.3% ADRs were possible. According to Anwikar et al.,[25] 96.49% ADRs were found to be possible and 3.50% probable by WHO probability scale. 20 (8.77%) were mild, 176 (77.19%) were moderate, and 32 (14.02%) were severe in nature. Only 2.63% ADRs were found to be preventable. A study by Bhuvana et al.,[26] the majority (89.24%) of ADRs were found to be possible, 93.05% were moderately severe (level 3) and 30.38% ADRs were preventable.

CONCLUSION

To conclude, HAART is responsible in halting and reversing the number of AIDS-related deaths but also associated with vivid adverse effects involving various body systems. Most ADRs are mild to moderate. Some of the adverse effects are inherently associated with ART drugs but many ADRs are still preventable to much extent. To prevent these and maintain adherence to treatment, ART should be judicially used with regular monitoring of ADRs.

ACKNOWLEDGMENTS

Author thankful to Dr. Rehan Alam for his continuous support for spontaneously reporting the ADR from the Department of ART Centre, RIMS, Ranchi, and it is author immense pleasure to thank our Pharmacovigilance associate Md Rashid Haider Khan for his co-operation in compiling the ADR reports.

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How to cite this article: Kumar A, Majhee L, Gari M. Causality, severity and preventability assessment of adverse drug reactions in patients received anti-retroviral therapy in a tertiary care hospital: A retrospective study. Natl J Physiol Pharm Pharmacol 2017;7(2):178-182.

Source of Support: Nil, **Conflict of Interest:** None declared.