

Study of adverse drug reactions to antiretroviral therapy in a tertiary care hospital, Tirupati

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Abstract

Purpose: Human immunodeficiency virus-infected patients do not adhere to their antiretroviral therapy (ART) due to adverse effects of drugs. The continuous monitoring of adverse drug reactions (ADRs) may ensure the safe use of drugs in patients. Hence, a retrospective analysis was carried out to assess the ADRs pattern, causality, and severity associated with various antiretroviral drug regimens in patients receiving ART.

Materials and Methods: A retrospective, analytical study was carried out at ART nodal center in Sri Venkateswara Ramnarain Ruia Government General Hospital, Tirupati. Data were collected by spontaneous reporting of health-care professionals from ART centers using Suspected ADR Reporting Forms of Indian Pharmacopoeia Commission to record the ADRs occurred in the patients who underwent treatment from December 2015 to November 2016. A total of 299 ADR reports were collected during the study period. The causality and severity of the reported ADRs were assessed using suitable scales.

Results: From a total of 299 ADR reports, females (63.81%) experienced higher ADRs than males (36.12%). The highest number of ADRs was reported to zidovudine/lamivudine/nevirapine (ZLN) regimen (76.92%) than tenofovir/lamivudine/efavirenz (TLE) regimen (23.07%). Cutaneous reactions were higher (34.34%) among patients receiving ZLN therapy, and drowsiness (53.62%) was the most common ADR in patients receiving TLE regimen. According to the World Health Organization causality assessment scale, most of the ADRs were possible (75.92%). On the assessment of Modified Hartwig and Siegel Severity Scale, 55.09% of ADRs were moderate.

Conclusion: The study showed an increased incidence of ADRs to ART which calls for efficient pharmacovigilance systems to improve patient care and drug safety.

Keywords: Adverse drug reactions, highly active antiretroviral therapy, pharmacovigilance

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INTRODUCTION

In the global scenario, the burden of adverse drug reactions (ADRs) is relatively high and accounts for considerable morbidity, mortality, extended hospital

stay, and increased health-care cost.^[1,2] According to the World Health Organization (WHO), ADR is defined as a response to a drug which is noxious and unintended, and which usually occurs at normal doses

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used in human for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function.^[3]

Human immunodeficiency virus (HIV) continues to be a serious health issue in many parts of the world. In the year 2017, the United Nations Programme on HIV and AIDS reported that 36.9 million people were living with HIV worldwide, and among them, 21.7 million were on antiretroviral therapy (ART).^[4]

India is the third largest HIV epidemic in the world after South Africa and Nigeria, with 49% accessing ART.^[5] Since the mid-1990s, the progression of HIV to AIDS and AIDS-related mortality has been fallen dramatically as a result of highly active ART (HAART).

India has made remarkable achievement in HIV control and management led by the National AIDS Control Organization. The Government of India, Ministry of Health and Family Welfare, provides free combination chemotherapy called HAART to the people infected with HIV. The establishment of treatment service facilities has also been scaled up to 519 ART centers and 1094 link ART centers that offer systemic HIV care, drugs at free of cost, and counseling centers for psychosocial support and management of ADRs with a deep emphasis on ART adherence.^[6]

The easy availability and use of ART from government setup dramatically reduced the disease-related morbidity and also increased the quality and life span of the patients. The ARTs have a greater impact on reducing HIV viral load and providing durable suppression of viral replication. ART converts HIV/AIDS from life-threatening condition to an easygoing chronic manageable condition with prolonged survival times.^[7] At present, there are six classes of antiretroviral drugs in ART which include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-NRTIs, protease inhibitors, fusion inhibitors, the CCR5 antagonists, and the integrase strand transfer inhibitors.^[8]

Despite this achievement from ART medications, it still remains a great challenge for both the physicians and the patients to continue the treatment regimen successfully. Strict adherence to the prescribed routine of ART is vital for the success of therapy and also to bring about a reduction of the viral load. Once the therapy has been initiated, it has to be continued throughout the life. However, 25% of the patients discontinue their initial drug regimen due to treatment failure (inability to suppress HIV viral replication

to below 50 copies/ μ l), ADRs, or noncompliance to the therapy.^[7] These adverse events may be acute or chronic, mild or serious, are relatively common phenomena affecting both individual patient's and public health.^[9] In addition to drug resistance and difficulty of adhering to complex regimens, ADR associated with HAART is a major concern. Monitoring and reporting of ADRs to ART in the Indian population are very important. The treatment itself may be long (for the lifetime), expensive, and troublesome at times due to ADRs.^[10]

To safeguard the health of 1.27 billion people of India, the Central Drugs Standard Control Organization, New Delhi, has initiated the Pharmacovigilance Programme of India (PvPI), which is coordinated by the Indian Pharmacopoeia Commission (IPC) located at Ghaziabad, Uttar Pradesh.^[11]

As a part of PvPI, ADR Monitoring Centre (AMC) was established in 2014 at Sri Venkateswara Medical College (SVMC)/Sri Venkateswara Ramnarain Ruia Government General Hospital (SVRRGGH), Tirupati, Andhra Pradesh, India. The national PvPI focuses to create sufficient awareness and adequate training about drug safety monitoring among health-care professionals.^[12]

Many research studies have been carried out in the African and Western population to study the ADR profile to ART; however, such studies are very scanty in south Indian population. In view of public health and patient safety, a study was conducted through spontaneous reporting of ADRs from ART center, SVRRGGH, Tirupati, to analyze the nature of ADRs to ART in HIV-positive patients. The spontaneous reporting leads to early detection of signals of new, rare, and serious ADRs and ensures the effective postmarketing surveillance of drug safety in the Indian population.

MATERIALS AND METHODS

The present retrospective study was carried by analyzing the spontaneous ADRs reported by health-care professionals from ART center to AMC of SVMC/SVRRGGH, Tirupati, Andhra Pradesh, India, during December 2015–November 2016.

All the patients diagnosed with HIV and on HAART identified with ADRs were included in the study. The study was initiated after approval obtained from the ART center and Institutional Ethics Committee SVRRGGH, Tirupati, by maintaining a strict confidentiality about patient details. Health-care professionals from the ART center used Suspected ADR Reporting (SADRR) Forms of IPC

to record the ADRs. The patient details (age, sex, weight, and initials), suspected adverse reaction (description of the event, date of start, and recovery), other relevant histories, seriousness, outcomes, relevant laboratory tests, suspected medications (dates of prescription, dose, frequency and route of administration, and duration and indication of use) and seriousness of the reaction, outcome of the reaction, use of concomitant medications, and additional information (ADR management) were extracted from the SADRR Forms.

Causality assessments were carried out as per the WHO-Uppsala Monitoring Centre (UMC) causality assessment scale, which classifies drug reactions into certain, probable, possible, unlikely, conditional, and unassessable ADR. Severity of the reaction was assessed using modified Hartwig and Siegel ADR Severity Assessment Scale, which classifies ADR into mild, moderate, and severe. Statistical analysis of the data was done using Microsoft Excel (Microsoft Office Professional 2016) and the results were expressed as numbers and percentage.

RESULTS

A total of 299 ADR reports exposed to ART were received at AMC. Among them, 63.81% were females and had a higher prevalence than males (36.12%), as shown in Table 1. The prevalence of ADRs was higher among the age group of 31–40 years (35.11%) followed by the age group of 41–50 years (31.4%). The highest number of ADRs was reported among the patients receiving zidovudine + lamivudine + nevirapine (ZLN) regimen (230, 76.92%) followed by tenofovir + lamivudine + efavirenz (TLE) regimen (69, 23.07%), as depicted in Figure 1. Among the patients receiving the ZLN therapy, the prevalence of ADRs was higher in females (66.5%) than in males (33.5%). The highest number of ADRs was observed in the age group of 31–40 years (35.22%) followed by the age group of 41–50 years, as shown in Table 2.

The agewise and system wise distribution of ADRs identified in patients on ZLN therapy was given in Table 3 and Figure 2. Among gastrointestinal ADRs, most common ADR was vomiting/nausea (19, 8.26%), followed by gastric irritation (7, 3.04%), loss of appetite (4, 1.73%), and abdominal discomfort or pain (3, 1.30%). Among the cutaneous reactions, the most common was hyperpigmentation of the skin (39, 16.9%), rash (35, 15.21%), and itching (5, 2.17%). In musculoskeletal- and connective tissue-related disorders, the most common was buffalo hump (22, 9.5%), followed by lipoatrophy (20, 8.69%) and myalgia (2, 0.86%). The other most common

Table 1: Baseline characteristics of patients who had experienced adverse drug reactions with antiretroviral therapy

Characteristics	n (%)
Gender	
Male	108 (36.12)
Female	191 (63.81)
Age (years)	
<10	2 (0.67)
11-20	11 (3.68)
21-30	46 (15.38)
31-40	105 (35.11)
41-50	94 (31.44)
51-60	31 (10.37)
>60	10 (3.34)

Table 2: Baseline characteristics of patients receiving zidovudine/lamivudine/nevirapine regimen

Characteristics	n (%)
Gender	
Male	77 (33.5)
Female	153 (66.5)
Age (years)	
<10	2 (0.87)
11-20	7 (3.04)
21-30	36 (15.65)
31-40	81 (35.22)
41-50	72 (31.30)
51-60	25 (10.87)
>60	7 (3.04)

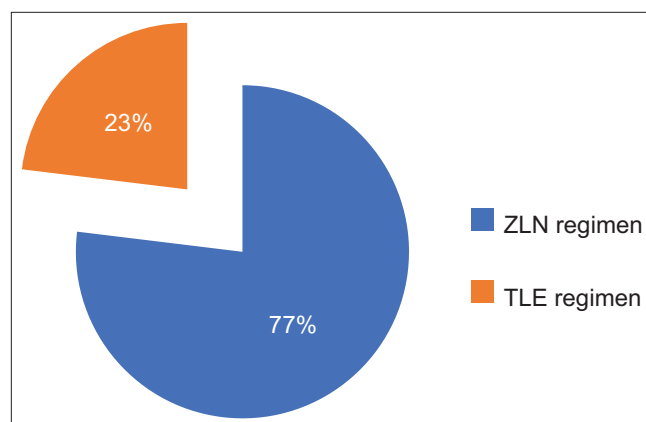


Figure 1: Antiretroviral therapy regimen and percentage of patients with adverse drug reactions

ADRs identified in patients receiving ZLN therapy were anemia (51, 22.17%), peripheral neuropathy (5, 2.17%), gynecomastia (4, 1.73%), and fever and iris (2, 0.86%).

The baseline characteristics and age wise distribution of ADRs in patients receiving TLE regimen were shown in Tables 4 and 5. Among the 69 patients receiving TLE therapy, the ADRs were more common in females (55.07%) than males (44.92%). The prevalence of ADRs was higher in the age group of 31–40 years (34.78%) followed by 41–50 years (31.88%). Among 69 ADRs identified in patients receiving

Table 3: Agewise distribution of adverse drug reactions identified in patients on zidovudine/lamivudine/nevirapine therapy

ADRs	Total	Male	Female	<10 yrs	11-20 yrs	21-30 yrs	31-40 yrs	41-50 yrs	51-60 yrs	>60 yrs
Gastrointestinal reactions										
Vomiting, nausea	19	5	14	0	0	7	5	6	1	0
Gastric irritation	7	6	1	0	0	0	2	2	2	1
Abdominal discomfort, pain	3	2	1	0	0	1	1	0	1	0
Diarrhea	4	2	2	0	0	1	0	2	1	0
Loss of appetite	4	2	2	0	0	0	1	2	0	1
Jaundice	5	0	5	0	0	4	1	0	0	0
Cutaneous reactions										
Rash	35	10	25	2	1	10	13	5	3	1
Hyper pigmentation of skin	39	22	17	0	1	3	15	13	5	2
Itching	5	2	3	0	0	1	2	2	0	0
Musculoskeletal and connective tissue disorders										
Myalgia	2	1	1	0	0	0	0	2	0	0
Buffalo hump	22	2	20	0	1	0	6	11	3	1
Lipoatrophy	20	1	19	0	0	0	14	5	1	0
Other adverse drug reactions										
Anemia	51	15	36	0	3	8	14	19	6	1
Peripheral neuropathy	5	1	4	0	0	0	2	3	0	0
Gynaecomastia	4	4	0	0	1	0	2	1	0	0
Fever	2	0	2	0	0	1	1	0	0	0
Iris	2	1	1	0	0	0	1	1	0	0

Table 4: Baseline characteristics of patients receiving tenofovir/lamivudine/efavirenz regimen

Characteristics	n (%)
Gender	
Male	31 (44.93)
Female	38 (55.07)
Age (years)	
<10	0 (0)
11-20	4 (5.80)
21-30	10 (46.49)
31-40	24 (34.78)
41-50	21 (31.88)
51-60	6 (8.70)
>60	3 (4.35)

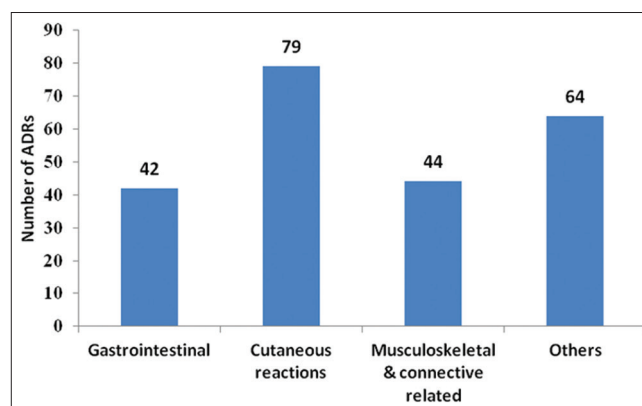
TLE regimen, drowsiness/giddiness (53.62%) was the most common ADR followed by headache (15.94%) and nightmares (8.69%).

To improve the quality of the findings of the study, causality assessment was carried out for individual cases using the WHO-UMC scale. The details of the causality assessment are given in Table 6. On assessment of the severity of ADRs by Hartwig *et al.* scale, it was evident that most of the ADR reported in the study, were of moderate severity. The details of the severity assessment are given in Table 7.

On the development of any ADR or intolerance towards the ART medication, suitable steps like change in regimen, symptomatic treatment or counselling regarding medications or both were done as indicated.

DISCUSSION

In the present study, of the 299 ADR reports, females (63.81%) had a higher prevalence of ADRs than

**Figure 2: System-wise distribution of adverse drug reactions identified in patients receiving zidovudine/lamivudine/nevirapine therapy**

males (36.12%). Similar results were found in the previous study by Patil *et al.*, and females were reported to have a higher incidence of ADRs (60.55%) than males (39.45%) in their study. In contrast to the study by Kiran *et al.*, males had a higher prevalence of ADRs as compared to female patients. Possible explanation for this gender difference in ADR incidence could be a gender-specific difference in body mass index, fat composition, drug susceptibility, hormonal effects, or genetic constitutional differences on the levels of various enzymes although the same has not been proven conclusively.^[12,13]

In the present study, the prevalence of ADRs was higher in 31–40 years (35.11%) followed by 41–50 years (31.4%). These results are in concordance with the previous study by Patil *et al.* This could be explained as most of the patients in the study belonged to the age group of 21–40 years. Therefore, the majority of ADRs were detected from this group, as

Table 5: Age-wise distribution of adverse drug reactions identified in patients receiving tenofovir/lamivudine/efavirenz therapy

Name of the ADR	Total	Male	Female	<10 years	11-20 years	21-30 years	31-40 years	41-50 years	51-60 years	>60 years
Drowsiness/giddiness	37	22	15	0	2	5	12	13	3	2
Headache	11	5	6	0	1	4	2	3	1	0
Nightmares	6	0	6	0	1	1	2	1	1	0
Loss of memory	2	0	2	0	0	0	1	1	0	0
Deafness/hearing impairment	3	0	3	0	0	0	1	0	1	1
Decrease in vision/blurred vision	3	1	2	0	0	0	1	1	1	0
Sleeplessness	5	3	2	0	0	0	3	2	0	0
Abnormal thinking	1	0	1	0	0	0	0	1	0	0
Depression	1	0	1	0	0	0	0	1	0	0

ADR=Adverse drug reaction

Table 6: Causality assessment using the World Health Organization-Uppsala Monitoring Centre Scale

	Assessment criteria	Percentage
Causality assessment	Certain	0.67
	Probable	23.41
	Possible	75.92

Table 7: Severity Assessment using Modified Hartwig and Siegel Scale

	Assessment criteria	Percentage
Severity assessment	Mild	41.99
	Moderate	55.09
	Severe	2.92

they are economically productive and sexually more active age group. On the contrary, Eluwa *et al.* reported that age and gender were not significantly associated with ADRs.^[12-14]

In our study, 77% of the ADRs were reported in patients who were on ZLN regimen followed by TLE regimen (23%). Patil *et al.* also found similar results, of all patients who reported ADRs, 74.3% were on ZLN regimen, whereas 34.3% were on TLE regimen.^[12]

Among ZLN regimens, most of the ADRs were cutaneous (34.34%) followed by anemia (22.17%) and musculoskeletal- and connective tissue-related disorders (19.13%) followed by gastrointestinal ADRs (18.26%). These results were in contrast to the previous study conducted by Kumari *et al.*, where gastrointestinal ADRs (28.91%) were higher in patients receiving ZLN regimen followed by neurological (27.16%), hematological (24.55%), and dermatological ADRs (11.83%).^[15]

In the present study, among ZLN therapies, anemia (22.17%) was the most commonly reported ADR followed by hyperpigmentation of the skin (16.95%) and skin rash (15.21%). These results are in concordance with previous study results by Patil *et al.* and Bhuvana *et al.* In these studies, anemia and skin rash were found to be the most common types of ADRs. This may be owing to bone marrow suppression action of zidovudine that leads to anemia and thrombocytopenia.^[12,16]

Nervous system-related disorders were the most commonly observed ADRs in patients receiving TLE regimen which includes drowsiness/giddiness (53.62%) followed by headache (15.94%) and nightmares (8.69%).

As per the WHO causality assessment scale, 75.92% of the ADRs were possible and 23.41% were probable. Severity assessment was carried out by modified Hartwig and Siegel Scale, in which most of the ADRs were moderate (55.09%) followed by mild (41.99%) and 2.92% severe.

CONCLUSION

HIV/AIDS is one of the most challenging therapies compared with other chronic diseases. With the increasing use of HAART, it is possible that there is an increased risk of drug-induced illness due to HAART. The prevalence of ADRs was more common on those patients taking ZLN followed by TLE regimen. As observed in this study, many ADRs are predictable and possibly preventable. Therefore, prompt recognition and early detection with efficient management of ADRs will reduce the economic burden and thereby improve the medication adherence resulting in better therapeutic outcomes.

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Conflicts of interest

There are no conflicts of interest.

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