

An assessment of adverse drug reaction patterns among HIV positive patients receiving antiretroviral therapy in a tertiary care hospital

Rita Kumari*, Satish Chandra, Manju Gari and Abha Kumari

Department of Pharmacology, Rajendra Institute of Medical Sciences (RIMS), Ranchi, India

QR Code



*Correspondence Info:

Dr. Rita Kumari
Junior Resident,
Department of Pharmacology,
Rajendra Institute of Medical Sciences (RIMS), Ranchi, India

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Abstract

Background and Objectives: Antiretroviral therapy (ART) has been proved efficacious in reducing morbidity and mortality related to Human Immunodeficiency Virus (HIV) infection, however, also associated with long and short term drug – induced toxicities. This study was conducted to monitor the adverse drug reactions (ADRs) associated with various antiretroviral drug regimens, its causality, severity and preventability assessment in patients receiving ART.

Methods: Using a prospective observational study design, 280 patients were enrolled for the study. The ADR monitoring was carried out for a period of one year (December 2015 - November 2016) in patients living with HIV (PLHIV) and receiving ART from an outpatient setting of nodal ART centre of Rajendra Institute of Medical Sciences, Ranchi (Jharkhand).

Results: A total of 280 patients were monitored by active surveillance. Out of them 228 patients identified of at least one or more ADRs. The most number of ADRs were observed with ZLN (Zidovudin + Lamivudin + Nevirapin) and ZLE (Zidovudin + Lamivudin + Efavirenz). The ADRs commonly found, GIT side effects (29%), CNS side effects (27%) and anaemia (25%). Tenofovir based regimens was safer than ZLN and ZLE.

Conclusion: Type of antiretroviral regimen and time since initiation of ART were associated in causality of related adverse reactions. This study addressed the added morbidity among HIV patients taking ART. With the increasing incidence of ADRs associated with antiretroviral chemotherapy, it requires proper monitoring and reporting to intervene at an early stage and modify the antiretroviral drug regimen (ARV) as per.

Keywords: Adverse drug reactions, Antiretroviral therapy, HIV / AIDS, Prospective observational study.

1. Introduction

The United Nations Programme on HIV and AIDS (UNAIDS) reported, 36.7 million people were living with HIV at the end of 2015 and 18.2 million were accessing antiretroviral therapy (June 2016) worldwide.[1] While in India, HIV prevalence was estimated 0.26%, and around 13.45 lakhs people were needed ART in 2015.[2]

The Government of India, Ministry of Health and Family Welfare, provides free combination chemotherapy, called Highly Active Antiretroviral Therapy (HAART) to the people infected with HIV. The easy availability and use of antiretroviral therapy from government setup, dramatically reduces the disease related morbidity as well

as increases the quality and life - span of the patients. These therapies have a greater impact on reducing HIV viral load and provide durable suppression of viral replication. Antiretroviral therapy makes the patient from life – threatening conditions to easy going chronic conditions.

Despite this achievement, from ART medications, it still remains a great challenge for both the treating physicians as well as the patients to continue the treatment regimen successfully. About 25% of patients discontinued their initial drug regimen due to treatment failure (inability to suppress HIV viral replication to below 50 copies / μ l), adverse reactions or noncompliance to the therapy.[3] Development of ADRs were highly affected on patient's

conditions such as malnutrition, tuberculosis and patients presenting with advanced HIV disease. Other risk factors also identified, that include patient age, gender, duration on treatment, disease biomarkers such as CD4 count, viral load and body mass index (BMI).[4,5] These adverse events, may be acute or chronic, mild or serious, which are relatively common phenomena affecting both individual patients and public health. In addition to drug resistance and the difficulty of adhering to complex regimens, side effects associated with highly active antiretroviral therapy have become a major concern.

Most of the adverse drug reactions remain unnoticed or not reported by the patients. Thus, continuous evaluation will be benefit of the ART that help to achieve ultimate goal of making the treatment more safe and effective to the patients.[6]

Therefore, this study was conducted for early recognition of drug regimen associated adverse reactions and assessment of their causality, severity and preventability. Thus the ultimate goal was early modification of drug regimen to improve patient’s compliance and tolerability to the therapy and reduction of morbidity and early mortality.

2. Methods

The study was conducted in an outpatient setting of nodal ART centre of Rajendra Institute of Medical Sciences, Ranchi (Jharkhand). The ethical approval was obtained from Institutional Ethics Committee before the initiation of study. A written informed consent was taken from the patients after explaining the study procedure.

A prospective observational study was designed and the ADR monitoring carried out for a period of one year (December 2015 - November 2016) in patients living with HIV and receiving antiretroviral therapy. A total of

280 patients enrolled for the study, from which 228 patients were observed at least one or more than one adverse drug events during the study period.

These patients were intensively monitored for any adverse clinical events during follow - up visits to the ART centre. Treatment naïve subjects of either sex, aged 18 years or above and receiving ART for more than six months of duration were included in the study. While the patients with any other co-morbidity like diabetes mellitus, hypertension, chronic kidney disease and pregnant women were excluded from the study.

Diagnosis of adverse events was made on the basis of patient’s complaints and/or from the patient’s attendants, their morphological changes during routine clinical examinations as well as a review of outpatient case records, laboratory reports, clinician’s notes and prescriptions at each follow – up visit. All the information was recorded in the adverse drug reaction reporting forms. Any other details regarding drug therapy and associated adverse events was obtained from the treating physician.

The World Health Organization (WHO) ADR probability scale and Naranjo algorithm were used for causality assessment.[7,8] Severity of ADRs was assessed by using the Modified Hartwig and Siegel scale.[9] In preventability assessment, ADRs were categorized into preventable or not preventable by using the criteria of Schumock and Thornton.[10]

3. Results

In this study, among 228 patients who were developed ADRs, 126 (45%) were males and 102 (36.42%) were females. (Fig.-1). Most of the patients were between the age group of 18 - 30 years (44.73%) followed by 31- 40 years (28.07%) (Fig.- 2).

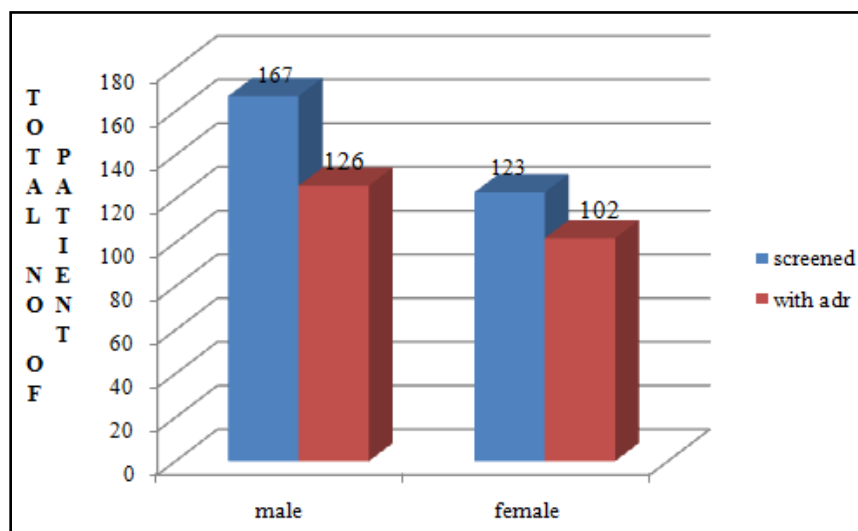


Figure 1: Total number of Males and Females presenting with ADRs

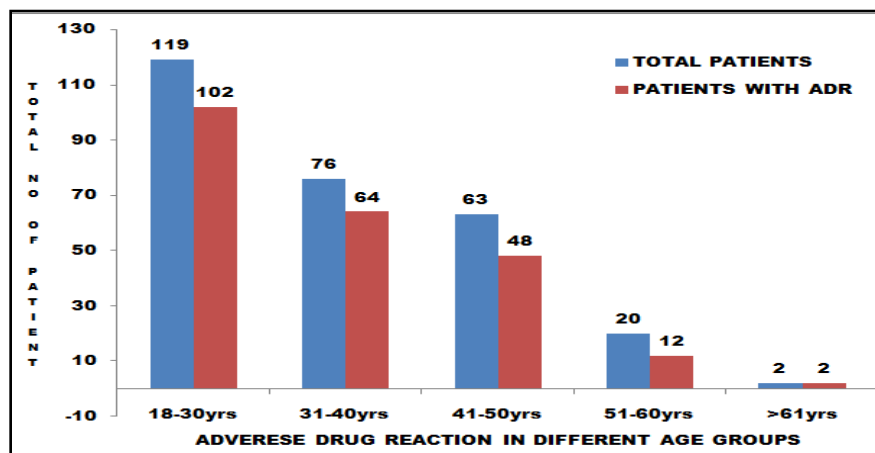


Figure 2: Patients with Adverse Drug Reactions in Different Age Groups

Among gastrointestinal ADRs most common ADR was nausea (20, 8.77%) followed by increased liver enzymes (12, 5.26%), abdominal pain (11, 4.82%), vomiting (8, 3.50%), diarrhea (5, 2.19 %) and anorexia (5, 2.19 %), gastric intolerance (3, 1.31%) and abdominal cramps (2, 0.87%). Among the nervous system associated ADRs the most common was insomnia (24, 10.52%) followed by headache (16, 7.01%), giddiness (5, 2.19%), nightmare (6, 2.63%), dizziness (4, 1.75%), peripheral neuropathy (4, 1.75%) and tremors (3, 1.31%). In skin and

subcutaneous tissue related, skin rashes (18, 7.89%) was most common ADRs followed by hyper pigmentation of skin and blackening of nails (6, 2.63%) and a few patients presented with severe drug eruptions of Stevens Johnson Syndrome (3, 1.31%). In musculoskeletal and connective tissue related ADRs were generalized weakness (11, 4.82%) and body ache (6, 2.63%). Blood and lymphatic system associated ADRs includes, anaemia (52, 22.80%) and pallor (4, 1.75%).

Table 1: Drug regimen associated ADRs

ADR Description	No. of Patients taking Drug Regimen				
	AZT+3TC+NVP	AZT+3TC+EFZ	TDF+3TC+EFZ	TDF+3TC+ATV+RTV	AZT+3TC+ATV+RTV
Gastrointestinal Disorders					
Anorexia	3	2	0	0	0
Nausea	3	4	6	3	4
Vomiting	2	2	3	0	0
Abdominal Cramps	1	1	0	0	0
Abdominal Pain	2	3	5	1	0
Diarrhoea	1	1	2	0	1
Gastric Intolerance	0	1	2	0	1
Increased Liver Enzymes	4	2	5	1	0
Nervous System Disorders					
Headache	7	5	1	0	3
Giddiness	0	3	2	0	0
Insomnia	10	8	4	1	1
Tremor	1	1	1	0	0
Peripheral Neuropathy	1	2	1	0	0
Nightmare	1	3	2	0	0
Skin And Subcutaneous Tissues					
Rashes	9	3	4	1	1
Pigmentations	4	1	0	0	1
SJS	3	0	0	0	0
Musculoskeletal And Connective Tissue Disorders					
Generalized Weakness	5	2	3	1	0
Body ache	2	1	1	1	1
Blood And Lymphatic System Disorders					
Anaemia	22	15	8	0	7
Pallor	2	1	0	0	1

In our study, most of the ADRs observed with ZLE regimen (Zidovudine + Lamivudine + Efavirenz) (31.57%) followed by ZLN regimen (Zidovudine + Lamivudine + Nevirapine) (21.05%), TLE regimen (Tenofovir + Lamivudine + Efavirenz), (19.73%), ZLAR regimen (Zidovudine + Lamivudine + Atazanavir + Ritonavir) (16.66%) and TLZR regimen (Tenofovir + Lamivudine + Zidovudine + Ritonavir) (10.96 %) (Figure - 3).

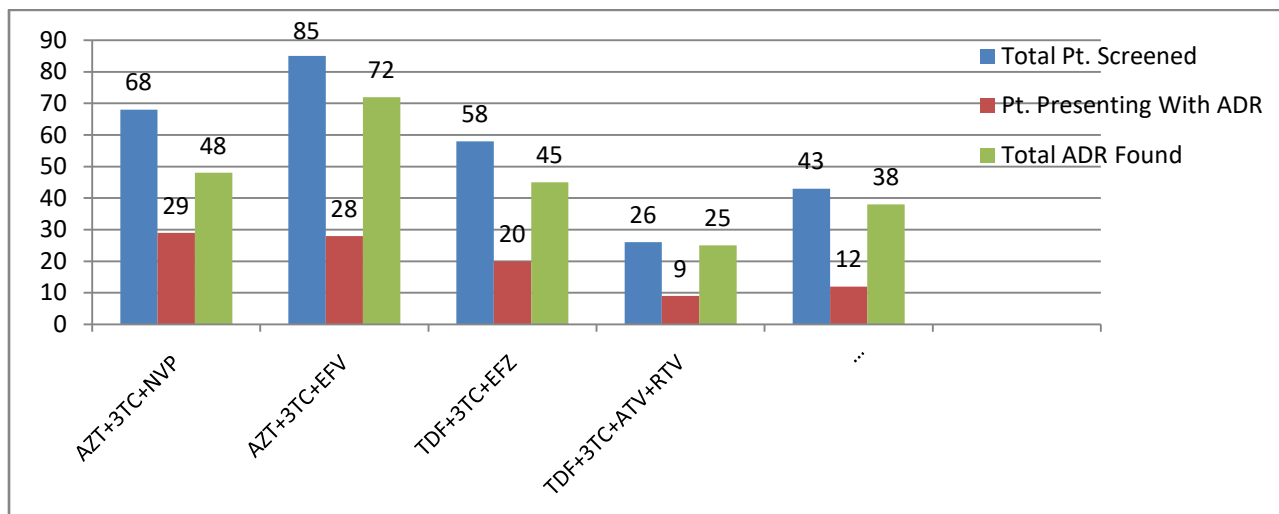


Figure 3: Drug Regimen and Patients Found with Adverse Drug Reactions.

Causality assessment was done by WHO causality assessment scale, where 201 patients presented with ADRs were probable (88%) and 27 patients were possible (12%). According to Naranjo’s algorithm, most common the ADRs were possible (132, 57.83%) and remaining were probable (96, 42.17%).(Fig.- 3)

Modified Hartwig and Siegel’s scale was used for severity assessment, where most of the patients were found to with “mild” ADRs (189, 83%) followed by “moderate” (36, 16%) that required change in their drug regimens and only 1% (3) had “severe” ADR (life - threatening Steven Johnson Syndrome and anaemia) and they required prolonged hospital stay and additional treatment. (Fig. -4)

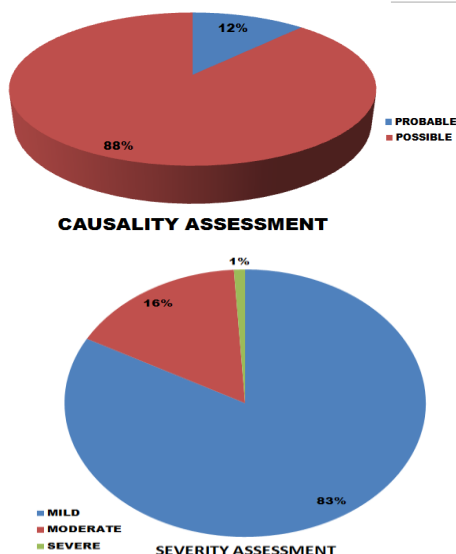


Figure 4: Causality and Severity Assessment of ADRs

In this study, preventability assessment was done by using Schumock and Thornton scale and it was found that most of the ADRs were non – preventable (190, 83.33%). Preventable ADRs were found only in 38 patients (16.66%). (Table -2)

Table 2: Schumock and Thornton Preventability Assessment

Preventability Assessment	Types	No. of ADRs	% of ADRs
	Non – Preventable		190
Preventable		38	16.66
Total		228	99.99

4. Discussion

This study explored the adverse drug reaction patterns associated with different combination regimens of antiretroviral therapy. Because this resulting in poor adherence and development of resistance to the therapy. Age, gender, type of ARV drug regimens, period of initiation of ART was found to be associated with HIV/AIDS drug related adverse reactions.

In this study, about 81.42% patients were presented with ADRs. Most of the ADRs were observed within 6 months of beginning of the therapy. The study also found higher prevalence of ADR in males (45%) than females (36.42%). Similar findings were reported by Anshu Kumar Jha et al, a higher prevalence in males (53.5%) compared to females (46.5%).[11] In contrast to Praveen Kumar et al reported that females (60.55%) had higher prevalence of ADRs than males (39.45%). [12] Our study reported that most of the patients were between the age

group of 18 - 30 years (44.73%) followed by 31- 40 years (28.07%). On the contrary, *Eluwa et al* reported that age and gender were not significantly associated with ADRs.[13] These variations may be due to study design, sample size, or demographic variations, hormonal effects, immunological status, drug susceptibility, drug metabolism and elimination, or genetic constitutional differences on the levels of various enzymes although the same has not been proven conclusively.[14]

Gastrointestinal (28.91%), neurological (27.16%), haematological (24.55%) and dermatological (11.83%) adverse drug reactions were commonly observed in this study. Majority of ADRs were reported by ZLE and ZLN based regimens. In our study, anaemia (52, 22.80%) reported and most of them were associated with Zidovudine based regimens. A study by *Kenneth et al* reported 4.3% cases of anaemia of which 94.5% were reported in patients who received Zidovudine - based regimens.[15] Similar results were found by *Bhuvana et al*, where anaemia (55.06%) was seen with Zidovudine .[16] This might be resulting from bone marrow suppression action of Zidovudine that leads to anaemia and thrombocytopenia.

Three cases of severe exfoliated; blistering rashes of Steven Johnson Syndrome (1.31%) with Nevirapine use were reported. Nevirapine was also found to be associated with other skin rashes, pigmentations and raised liver enzymes. Nevirapine associated of Steven Johnson syndrome was also reported by *Ward H et al*.[17] The cutaneous hypersensitivity reactions commonly observed in patients receiving antiretroviral therapy. Thus, early detection, withdrawal of suspected drugs, identification of causative agents and appropriate treatment of associated adverse events are essential for the prevention of additional exposure as well as disease progression.

Efavirenz use was observed as a risk factor for peripheral neuropathy, insomnia, giddiness and other central nervous system problem whereas hyperbilirubinemia found only in one patient with atazanavir – containing HAART regimen in our study. *R Rajesh et al* found a total of 3.1% of patients developed elevated indirect bilirubin levels with atazanavir - containing HAART regimen.[18]

Due to high rates of ARV therapy associated ADRs, the patients are now using Tenofovir (TDF) containing regimen as a first line ARV treatment. This regimen had been found with lower ADR rates in this study. Similar results were found by *Lieketseng et al*, Tenofovir (TDF) containing regimen was used as a first line ARV treatment because other regimens (ZLN/ZLE) have high rates of ADRs.[19] . More pharmacovigilance studies are needed to compare ADRs among patients on TDF containing regimen and patients on AZT + 3TC +

NVP/EFV, as TDF containing regimen found with lower ADR rates in this study.

In causality assessment, 88% of the ADRs were “probable” and 12% were “possible” according to WHO causality assessment scale, while Naranjo’s algorithm showed 57.83%, “possible” and remaining 42.17%, were “probable”. The similar findings observed by *Aboubacar A. Oumar et al*, in their study.[20] In our study, severity assessment done by modified Hartwig and Siegel’s scale, where most of the ADRs were “mild”(83%) followed by “moderate” (16%) and only 1% was “severe” type. Two important factors; decreased immunological states and multiple drug intakes had been found to be associated with severity of drug reactions. By using Schumock and Thornton scale of preventability assessment, 83.33% of ADRs were “non – preventable” and rest 16.66% were preventable. Study by *Padmavathi. et al*, also reported that most of the ADRs were non - preventable (87%).[21] As the most of adverse effects observed , were “ mild ” which might be related with therapeutic doses of drugs or the immunological conditions of the patients. Thus, majority of adverse effects could not be preventable in our study.

5. Limitations

This study had some limitations. Due to limited resources, no detailed investigations could be ordered apart from routine laboratory investigations. Another limitation was the lack of adherence data, which has been found to affect the rate of ADRs due to inadequate treatment uptake. The study was conducted for a short period at a single centre with a small sample size, thus the data cannot be representative of national statistics.

6. Conclusion

Studies related to HIV/AIDS indicate that high levels of adherence are necessary for prevention of drug resistance, viral suppression, and disease progression. [21] An adherent patient being one who takes >95% of prescribed drug doses. Thus to achieve the goals of highly active antiretroviral therapy (HAART), high levels of adherence are required. [22]

Thus, the findings of our study suggest that the treating clinicians must focus on early detection and prevention of ADRs in HIV infected patients receiving ART that will help to modify their drug regimens and to provide better adherence to antiretroviral therapy. This will help to reduce HIV/AIDS–related mortality and morbidity by transforming the disease into a chronic treatable condition. More proactive pharmacovigilance surveillance are required for better understanding, and timely reporting of ADRs, especially of problematic regimen and patients subgroups.

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