

Current pattern of adverse drug reactions to anti-retroviral therapy in an antiretroviral therapy centre attached to a government medical college of Maharashtra, India: a retrospective study

Praveenkumar T. Patil^{1*}, Mayur P. Pawar², Nimish R. Halasawadekar¹, Mayur P. Shinde¹, Arvind V. Kumbhar¹, Mamta S. Rathod³

¹Department of Pharmacology, GMC, Miraj, Maharashtra, India

²Department of Pharmacology, SBH GMC, Dhule, Maharashtra, India

³Department of Community Medicine, GMC, Aurangabad, Maharashtra, India

Received: 11 September 2016

Accepted: 15 October 2016

***Correspondence to:**

Dr. Praveen Kumar T. Patil,
Email: drpraveentpatil@yahoo.in

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Antiretroviral drug therapy (ART) has brought a ray of hope to people living with HIV/AIDS. Adverse drug reactions (ADRs) can often cause significant morbidity among individuals on ART, occasionally leading to mortality. The present study was conducted to assess the nature, causality, severity of ADRs to ART, and to identify risk factors for ADRs in HIV-positive patients receiving ART in India.

Methods: A total of 109 patients reported with ADRs to ART during July 2015-December 2015 were randomly included in a retrospective observational study conducted at an ART center attached to a government medical college of Maharashtra. Causality and severity assessment of ADRs was done by using Naranjo's ADR Causality scale and Modified Hartwig and Siegel scale respectively. The data was computed using MS Excel and descriptive results were expressed as counts and percentages. The study was approved by Institutional Ethics Committee.

Results: Among 109 patients, females (60.55%) had higher prevalence of ADRs than males (39.45%). A total of 132 ADRs were reported. Anemia (76.52%) was the commonest ADR reported followed by skin rash (11.36%) and raised renal function tests (6.06%). Zidovudine + Lamivudine + Nevirapine (ZLN) were the commonest ART regimen causing anemia as ADR.

Conclusions: Reporting of ADRs is a very inefficient system in detecting drug-related conditions, leading to underestimation of the burden due to ADRs in India. A well-structured, efficient pharmacovigilance systems, which assesses and monitor safety profile and impact of antiretroviral medicines is very much needed at present in India.

Keywords: Antiretroviral therapy, ADRs, HIV/AIDS, Pharmacovigilance

INTRODUCTION

It is estimated that presently 33.5 million people are living with human immunodeficiency virus (HIV) infection.¹ Antiretroviral drug therapy has brought a ray of hope to people living with HIV. Unfortunately, the adverse effects of these drugs are of serious concern globally as it is a major cause of medication non-adherence, leading to treatment failure.²

In spite of high disease burden, India has made remarkable achievement in HIV control and management, led by National AIDS Control Organization

(NACO). As of December 2015, NACO runs 516 antiretroviral therapy (ART) centers nationwide that offer systematic HIV care, drugs free of cost, and most importantly, a detailed counselling for psychosocial support and management of adverse reactions, with a deep emphasis on ART adherence.³

Presently there are 6 major classes of antiretroviral drugs which include more than 20 approved drugs. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), the non-nucleoside reverse transcriptase inhibitors (NNRTIs), the protease inhibitors (PIs), the fusion inhibitors (FIs), the CCR5

antagonists, and the integrase strand transfer inhibitors (INSTIs).⁴

The widespread accessibility of antiretroviral therapy has transformed HIV into a chronic manageable disease with prolonged survival times. As with any chronic therapy, drug related toxicities remain a major challenge in resource-limited settings due to a limited formulary and inadequately trained personnel.^{5,6}

The documented side effects of antiretroviral drugs are: Zidovudine causes bone marrow suppression leading to anemia and neutropenia. Stavudine causes nausea, peripheral neuropathy, pancreatitis and lipoatrophy. Nevirapine causes skin rash, SJ syndrome and hepatitis. Efavirenz causes malformations in foetuses so contraindicated in pregnancy. Skin rash occurred in 10% of patients. Lamivudine has minimum toxicity. Most common adverse effects of lamivudine were diarrhoea, malaise, fatigue, headache, and sleep disturbances.⁷

Adverse drug reactions (ADRs) can often cause significant morbidity among individuals on ART, occasionally leading to mortality. Unfortunately, up to 25% of all patients discontinue their initial ART regimen because of toxic effects or noncompliance within the first 6-8 months of therapy.⁸ Indeed, these drug toxicities can add an extra layer of complexity in the management of HIV by impairing patient adherence to treatment, leading to inferior clinical outcomes and higher cost to the public health system.^{9,10}

In this context, it becomes critical to have a deep understanding of factors that can contribute towards treatment success. The National Pharmacovigilance Programme of India, however, lacks continuity. There is insufficient awareness and inadequate training about drug safety monitoring among health care professionals in India. Often, ADRs go unnoticed or are not reported. Monitoring and reporting of ADRs to ART in the Indian population are very important. To our knowledge, there are not many systematic studies conducted in India concerning ADRs in HIV patients receiving ART. Hence the present study was conducted to assess the nature, causality, severity of ADRs to ART, and to identify risk factors for ADRs in HIV-positive patients receiving ART in India.

METHODS

A retrospective study was conducted at an anti-retroviral therapy (ART) Centre attached to SBH Government Medical College, Dhule, Maharashtra which was National AIDS control organization (NACO) approved. Out of 151 HIV/AIDS Patients (old and new cases) receiving highly active anti-retroviral therapy (HAART) during July 2015-December 2015 who were randomly included in the study, 109 patients had experienced more than one ADRs. Pediatric and Pregnant women receiving anti-retroviral therapy were excluded from the study.

Patient’s details such as name, age, sex, marital status, mode of transmission, CD4 count, ART regimens and adverse events (AEs) to the anti-retroviral drugs were collected from the case record sheets maintained in the ART Centre. Causality assessment of AEs by using Naranjo’s ADR Causality scale and the severity assessment of ADRs was done by using Modified Hartwig and Siegel scale.^{11,12} The data was computed using MS Excel and descriptive results were expressed as counts and percentages. The study was approved by Institutional Ethics Committee.

All the information collected was kept confidential and the identity of the HIV/AIDS patients was not disclosed.

RESULTS

Among 109 patients, females (60.55%) had higher prevalence of ADRs than males (39.45%).

Table 1: Baseline characteristics of patients who had experienced ADRs with antiretroviral therapy.

Characteristics	n	Percentage
Gender	Male	43 39.45
	Female	66 60.55
Age	15-25	12 11
	26-35	56 51.38
	36-45	29 26.61
	46-55	9 8.27
	56-65	3 2.75

The prevalence of ADRs was higher among 26-35 years age group (51.38%) followed by 36-45 years age group (26.61%) (Table 1).

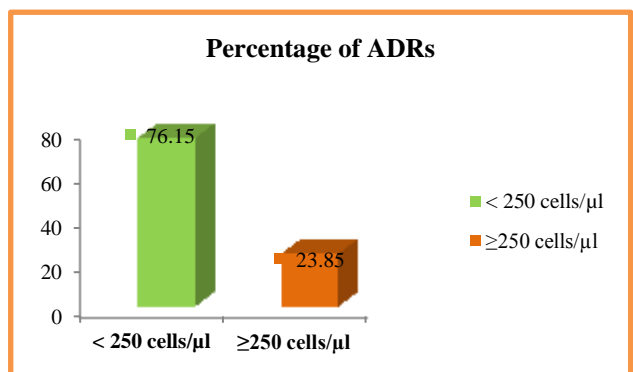


Figure 1: Comparison of ADRs with CD4 count of patients receiving antiretroviral therapy.

The higher number of ADRs were reported among patients receiving Zidovudine + Lamivudine + Nevirapine (ZLN) regimen (74.31%) followed by Stavudine+ Lamivudine + Nevirapine/Efavirenz (SLE/N) (10.09%), Tenofovir + Lamivudine + Efavirenz/ Nevirapine (TLN/E) (9.17%) regimen (Table 2).

Table 2: ART regimen and number of patients with ADRs with the regimen.

ART regimen	Number of patients with ADRs with the regimen	Percentage
ZLN	81	74.31
SLE/N	11	10.09
TLN/E	10	9.17
ZLE	7	6.42

Figure 1 show, patients with CD4 count <250 cells/ μ l (76.15%) had higher incidence of ADRs than patients with CD4 count \geq 250 cells/ μ l (23.85%) (Table 3).

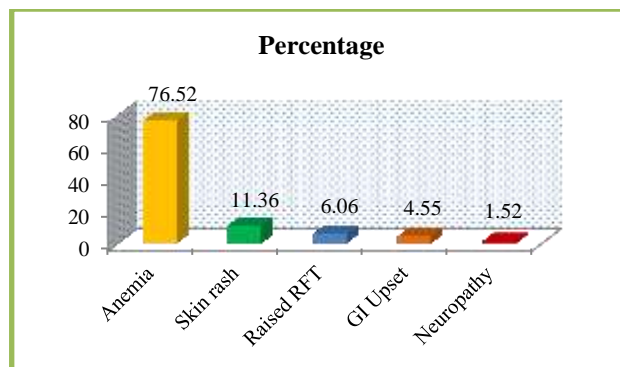


Figure 2: ADR pattern in patients receiving antiretroviral therapy (n = 132).

Out of 132 ADRs reported, Anemia (76.52%) was the commonest ADR reported followed by skin rash (11.36%) and raised renal function tests (6.06%) (Figure 2).

Table 3: Characteristics details of adverse drug reactions among patients receiving HAART.

ART regimen	Anemia	Skin rash	Raised RFT	GI and hepatobiliary related	Neuropathy
ZLN	75 (56.82%)	9 (6.82%)	3 (2.27%)	6 (4.55%)	----
SLN	8 (6.06%)	2 (1.52%)	1 (0.76%)	----	2 (1.52%)
ZLE	7 (5.30%)	1 (0.76%)	1 (0.76%)	----	----
TLN	5 (3.79%)	1 (0.76%)	3 (2.27%)	----	----
TLE	4 (3.03%)	1 (0.76%)	----	----	----
SLE	2 (1.52%)	----	----	----	----
ALN	----	1 (0.76%)	----	----	----

Total no of ADRs reported =132

Zidovudine + Lamivudine + Nevirapine (ZLN) were the commonest ART regimen causing anemia as ADR (Table 3).

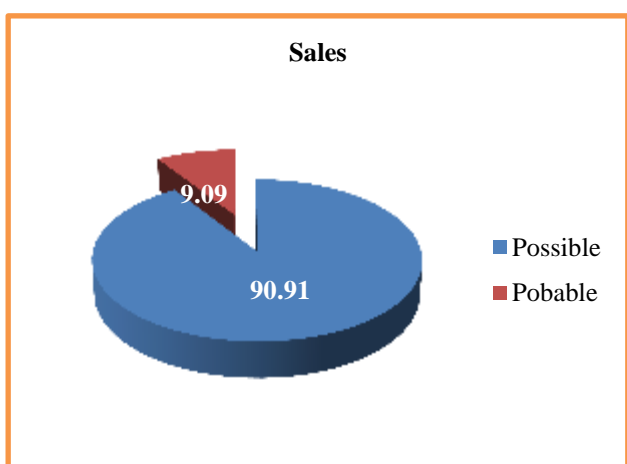


Figure 3: Causality assessment of ADRs reported among patients receiving antiretroviral therapy by using Naranjo's causality assessment scale.

On doing causality assessment, 90.91% ADRs belong to possible category followed by Probable (9.09%) (Figure 3) and 68.94% of the ADRs were of moderate followed by mild (30.30%) grade severity (Figure 4).

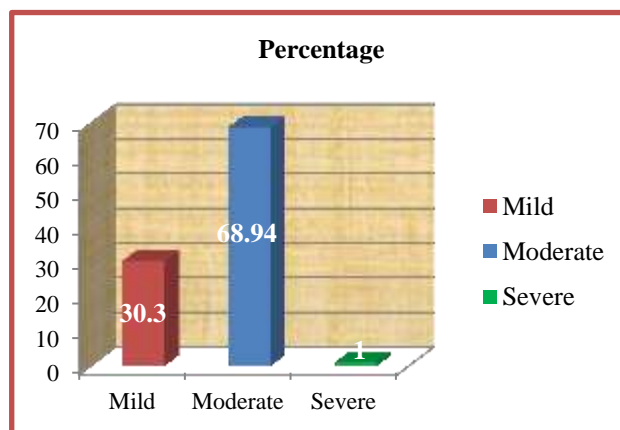


Figure 4: Severity assessment of ADRs reported among patients receiving HAART by using modified Hartwig and Siegel scale.

DISCUSSION

In the present study, females (60.55%) had higher prevalence of ADRs than males (39.45%). Similar results were found in previous study by Patel NM et al. females were reported to have higher incidence of ADRs (1.80 ADR per patient, 117/65) than males (1.57 ADR per patient, 157/100). But in study by Kiran Reddy AV et al. males had 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 on drug metabolism and elimination, or genetic constitutional differences on the levels of various enzymes although the same has not been proven conclusively.¹³⁻¹⁵

In the present study, the prevalence of ADRs was higher in 26-35 years (51.38%) followed by 36-45 years age group (26.61%). These results are in concordance with previous study results by Kiran Reddy AV et al. This could be explained as most of the patients in the study were belonged to the age group of 21-40 years.¹⁴ Therefore we might have detected majority of ADRs from this group as they are economically productive and sexually more active age group.

In our study, 76.15% of the ADRs were observed in patients who had baseline CD4 count < 250 cells/ μ l. Similar results were observed in a study from Kadapa, India that patients with CD4 count of <250cells/ μ l was affected with more ADRs.¹⁶

ADR to ART may depend on the baseline CD4 T- cell count at initiation of therapy. CD4 T- cell count may suggest that some complications were more frequent and severe when therapy is started at lower CD4 T cell counts. So we recommend doing CD4 count estimation at all ART center before initiating ART which might reduce the morbidity, mortality and socio-economic burden on the patient and society as well.¹⁷

In the present study, 74.31% of ADRs were reported in patients who were on Zidovudine/Lamivudine/Nevirapine (ZLN) regimen followed by Stavudine/Lamivudine/Nevirapine regimen (10.09%). Agu KA et al. Study by Agu KA et al. also found similar results, of all patients who reported ADRs, 39.9% were on Zidovudine/Lamivudine/Nevirapine (ZLN) regimen, while 34.3% were on Stavudine/Lamivudine/Nevirapine regimen (SLN).¹⁸

In the present study, Anemia (76.52%) was the most commonly reported ADR followed by skin rash (11.36%). These results are in concordance with previous study results by Bhuvana KB et al. In that study, anemia (55.06%) and rash (25.3%) were found to be most common type of ADRs.¹⁹

In the present study, Anemia was the most commonly reported ADR in patients who were on Zidovudine based regimen and Skin rash was commonly reported in patients on Nevirapine based ART regimen. Similar results were found by Bhuvana KB et al. where anemia (55.06%) was seen with ZLN regimen, an improvement in the Hb level was observed on discontinuation of Zidovudine based regimen. Skin Rash (25.31%) was seen with the Nevirapine based regimen.¹⁹

In a study by Kiran Reddy AV et al, the most commonly reported ADRs were (13.13%) gastritis, (8.75%) rashes, (8.13%) anemia, (7.5%) maculopapular rashes, (6.87%) giddiness, (6.87%) anorexia and (3.75%) parasthesia of legs.¹⁴ This could be due to under reporting or lack of awareness in the physicians, nursing staff and patients itself. So we recommend a pharmacovigilance system for creating awareness, reporting of ADRs due to ART as we found poor ADR reporting and variant results from the previous studies.

Causality assessment using standard methods is one of the best ways to establish the causal relationship between a drug and adverse events. In the present study, on doing causality assessment using Naranjo's ADR Causality scale, 90.91% of ADRs were belonging to possible category and 9.09% ADRs belongs to probable category. Similar results were found in a study conducted by Bhuvana KB et al. where majority ADRs were found to be possible category (89.24%).¹⁹

In order to take proper initiatives towards the management of ADRs, it is necessary to study the severity of ADRs. Modified Hartwig's and Siegel scale is widely used for this purpose which categorizes ADRs into mild, moderate and Severe. In the present study, 68.94% of ADRs were Moderate followed by mild (30.30%) and severe (0.76%). Results are in concordance with the study conducted by Patel NM et al. They found most of the ADRs were moderate (88.69%) followed by mild (8.39%) and severe (2.92%) according to modified Hartwig and Siegel scale.¹³

CONCLUSION

Studies on risk factors, ADR pattern to antiretroviral therapy and reporting of ADRs in ART centers appear to be lacking in our country. Thus the present study provides a baseline data regarding the demographic characteristics of patients who had ADRs, risk factors, ART regimens causing ADRs, ADR profile to various ART regimens among HIV positive patients registered at our ART Centre. ZLN was the most common ART regimen reported with ADR followed by SLN.

Monitoring safety and toxicity related to ART remains a challenge facing the public health sector. Spontaneous reporting of ADRs is a very inefficient system in detecting drug-related conditions, leading to underestimation of the burden due to ADRs. So we

recommend more systematic and more robust surveillance methods including structured pharmacovigilance systems, which assess and monitor safety profile and impact of antiretroviral medicines. This should facilitate the management of an individual patient to a greater level of satisfaction.

More research is needed to develop low-cost investigations and algorithms for prediction of adverse effects of existing regimen, along with generation of more efficacious and less toxic drugs.

The present study has some limitations. The period of study was not sufficient to assess long term adverse effect profile as HIV/AIDS patients living longer with ART. The study was conducted in only one nodal ART center attached to a remote government medical college of Maharashtra. These may exclude the actual number of HIV infected patients who were on ART and experienced ADRs.

Furthermore, we have not shown statistical significance among the parameters and large study sample must be needed for interpretation of results and to arrive at a definite conclusion. But it was our sincere effort and the results thus obtained would give feedback to clinicians and the health care decision makers regarding compliance of the treatment offered with regard to the national guidelines and thus promoting rational drug use.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- Oumar AA, Diallo K, Dembélé JP, Samaké L, Sidibé I, Togo B et al. Adverse Drug Reactions to Antiretroviral Therapy: Prospective Study in Children in Sikasso, Mali. *J Pediatr Pharmacol Ther.* 2012;17:382-8.
- Cooper CL, Breau C, Laroche A, et al. Clinical outcomes of first antiretroviral regimen in HIV/hepatitis C virus co-infection. *HIV Med.* 2006;7(1):32-7.
- National AIDS Control Organisation Annual Report, 2015-2016. Department of AIDS Control. Ministry of Health and Family Welfare, New Delhi. Available: <http://www.naco.gov.in/upload/2015%20MSLNS/List%20of%20ART%20Centres%20for%20Web.pdf> Accessed 1 August 2016.
- Prakashraju GJK, Chowta MN, Rather ZA, Mubeen F. The Pattern of the Initial Anti-retroviral Drug Regimens in HIV Patients at a Tertiary Care Hospital. *Journal of Clinical and Diagnostic Research.* 2012;6: 1178-80.
- Murphy RA, Sunpath H, Kuritzkes DR, Venter F, Gandhi RT. Antiretroviral therapy-associated toxicities in the resource-poor world: the challenge of a limited formulary. *J Infect Dis.* 2007;196(Suppl 3):S449-56.
- Max B, Sherer R. Management of the adverse effects of antiretroviral therapy and medication adherence. *Clinical Infectious Diseases.* 2000;30(Suppl 2):S96-116.
- Divakar B, Mistry SD, Kantharia ND, Mamtarani. The study of adverse drug reactions (ADR's) in HIV patients taking highly active antiretroviral therapy in ART centre, NCH, Surat, India. *Int J Med Pharm Sci.* 2012;03:9-18.
- Monforte AA, Lepri AC, Rezza G, Pezzoti P, Antinori A, Phillips AN et al. Insights into the reasons for discontinuation of the firstly highly active anti retro viral therapy (HAART) regimen in a cohort of antiretroviral naïve patients: Italian cohort of antiretroviral naïve patients. *AIDS.* 2000;14:499-507.
- O'Brien ME, Clark RA, Besch CL, Myers L, Kissinger P. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr.* 2003;34:407-14.
- Cicconi P, Cozzi-Lepri A, Castagna A, Trecarichi EM, Antinori A. Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naïve patients. *HIV Med.* 2010;11:104-13.
- Zaki SA. Adverse drug reaction and causality assessment scales. *Lung India.* 2011;28:152-3.
- Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm.* 1992;49:2229-32.
- Patel NM, Vaniya HV, Agrawal JM, Balat JD, Singh AP, Trivedi HR. Adverse drug reaction monitoring on antiretroviral therapy in human immunodeficiency virus patients in a tertiary care hospital. *Int J Basic Clin Pharmacol.* 2015;4:907-11.
- Kiran Reddy AV, Lihite RJ, Lahkar M, Choudhury U, Baruah SK. A study on adverse drug reactions in hiv infected patients at a art centre of tertiary care hospital in guwahati, india. *Asian J Pharm Clin Res.* 2013;6(Suppl 2):102-4.
- Rajesh R, Vidyasagar S, Nandakumar K. Highly active antiretroviral therapy induced adverse drug reactions in Indian human immunodeficiency virus positive patients. *Pharmacy Practice.* 2011;9(1):48-55.
- Srikanth BA, Babu SC, Yadav HN, Jain SK. Incidence of adverse drug reactions in human immune deficiency virus positive patients using highly active antiretroviral therapy. *J Adv Pharm Technol Res.* 2012;3(1):62-7.
- Bhatnagar S, Sharma H, Sharma VK. Study of adverse effects of anti-retroviral therapy in hiv naïve patients and their association with cd4 cell count. *Asian J Pharm Clin Res.* 2013;6:122-3.
- Agu KA, Isah MA, Oqua D, Habeeb MA, Agada PO, Ohiaeri SI. Incidence of Adverse Drug Reactions

in Patients on Antiretroviral Therapy: A study of Pharmaceutical Care in HIV Interventions in Nigeria. *West African Journal of Pharmacy*. 2013;24:30-42.

19. Bhuvana KB, Hema NG, Sangeetha. A prospective observational study of adverse drug reactions to

antiretroviral therapy: type and risk factors in a tertiary care teaching hospital. *Int J Basic Clin Pharmacol*. 2014;3:380-4.

Cite this article as: Patil PT, Pawar MP, Halasawadekar NR, Shinde MP, Kumbhar AV, Rathod MS. Current pattern of adverse drug reactions to anti-retroviral therapy in an antiretroviral therapy centre attached to a government medical college of Maharashtra, India: a retrospective study. *Int J Basic Clin Pharmacol* 2016;5:2438-43.