

A retrospective study to determine adverse effects of anti-retroviral agents in tertiary care hospital in Central India

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Abstract

Introduction: The introduction of Highly Active Anti-retroviral Therapy (HAART) has led to significant reduction in AIDS related morbidity & mortality. The majority of drugs available today are costly & have serious adverse effects, undesirable drug interactions & have to be taken lifelong. Though Anti-retroviral Therapy (ART) has increased lifespan of HIV positive patients, adverse drug reactions (ADRs) of this therapy still remains a major concern.

Objective: To collect demographic details & to assess incidence & causality of ADRs in HIV positive patients receiving ART.

Materials and Method: A retrospective observational study was carried out for a period of 18 months (1st January 2014 to 30th June 2015) at Government Medical College & Hospital, Nagpur. The ADRs reported by physician were collected, analysed & causality assessment was done.

Result: Out of 85 patients evaluated, 58 (68.3%) were females. ADRs reported were rash (40.6%), anemia (26.0%), nausea (16.7%), dizziness (6.3%), vomiting (5.2%), gastritis (3.2%), Steven Johnson Syndrome (1.0%) & diarrhoea (1.0%). Out of 96 ADRs reported, 39 (40.6%) were related to skin. Use of Zidovudine + Lamivudine + Nevirapine regimen reported majority of ADRs. Sixty one (67%) regimens were dechallenged, 29 (31.9%) regimens were continued while only 1 (1.1%) regimen was rechallenged. Seventy six (79.2%) ADRs were probable & 1 (1.0%) was definite as assessed by Naranjo's Causality Assessment Scale.

Conclusion: Rash was commonly reported ADR from ART. The findings from study suggests that there is need for intensive monitoring of ADRs in ART centre of Government Medical College & Hospital (GMCH), Nagpur.

Keywords: Anti-retroviral Therapy (ART), Adverse Drug Reactions (ADRs), Retrospective Observational Study, Causality assessment, Central India.

Introduction

Acquired Immunodeficiency Syndrome (AIDS) is a global epidemic. Since the beginning of the epidemic, more than 70 million people have been infected, of which approximately 35 million people have died of HIV-AIDS. An estimated 0.8% of adults aged 15–49 years worldwide are living with HIV. Sub-Saharan Africa remains most severely affected, with approximately 70% of the people living with HIV worldwide.⁽¹⁾ The total number of people living with HIV (PLHIV) in India is estimated at 21.17 lakhs in 2015. National adult HIV prevalence was estimated at 0.26% in 2015.⁽²⁾

Growing socio-economic burden of the disease led to the inception of National AIDS Control Organization (NACO) in the year 1986, under the aegis of Government of India, Ministry of Health and Family welfare and subsequently, the formation of National AIDS program in the year 1987.⁽³⁾ The Human Immunodeficiency Virus (HIV) has changed from fatal to chronic condition due to the easy and early availability of antiretroviral treatment (ART) among HIV positive patients through ART centres in Government Hospitals.⁽⁴⁾

As per the world health organization (WHO) recommendations, the initial HAART regimen should contain two nucleoside reverse-transcriptase inhibitors

(NRTIs) (lamivudine [3TC] or emtricitabine [FTC]), and other zidovudine [AZT] or tenofovir disoproxil fumarate [TDF] plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI) (either nevirapine [NVP] or efavirenz [EFV]) or an integrase inhibitor (INSTI) (Raltegravir).⁽⁵⁾

Although starting the HAART early has its own advantages, there are also potential disadvantages like long-term toxicity and development of anti-retroviral resistance. While HAART improves the quality of life among symptomatic patients, it is also associated with significantly reduced quality of life in some patients. Adverse effects have been reported with all ARV drugs and are amongst the most common reasons for switching or discontinuing therapy as well as for medication non-adherence.⁽⁶⁾

The HAART is the only treatment option for treating the HIV-positive patients for improving the immune system by increasing the number of CD4 cells essential to protect body from infections and cancers.⁽⁷⁾

There is paucity of pharmacovigilance data in Indian HIV positive patients on HAART therapy. Thus, the present study was performed with the aim to evaluate the incidence of ADRs related to ART in Central India i.e. Government Medical College Nagpur, and to retrospectively assess the causality, severity and preventability of ADR in HIV-AIDS patients.

Materials and Method

This was a retrospective study conducted at the antiretroviral treatment centre of Government Medical College Nagpur, India. The study was approved by Institutional Ethics Committee of Government Medical College Nagpur, India (No. EC / Pharmacy / GMC / NGP / 668). HIV-positive patients with fixed dose of HAART were included. The study was carried out for a period of 18 months (1st January 2014 to 30th June 2015) at Government Medical College & Hospital, Nagpur. The ADRs reported by physician were collected, analysed & causality assessment was done.

Records of all newly registered HIV patients (i.e. 1448) on HAART therapy of either gender were screened and patients with atleast one ADR reported by physician were included in the study. Patients receiving anti-tubercular treatment, those with opportunistic infections and pregnant women were excluded from the study.

Demographic details (Table 1) of patients were collected and it included - gender, age, weight, residence, education, occupation details and average monthly income; personal and family history (Table 2) included marital status, risk factors for HIV infection and family members positive for HIV; ART regimen used and susceptible ADRs observed were recorded in a specially designed case record form.

The causality was assessed with the help of Naranjo's ADR probability scale.⁽⁸⁾ Severity was assessed by Modified Hartwig and Siegel's Scale.⁽⁹⁾ Preventability was assessed by Modified Schumock and Thornton's Scale.⁽¹⁰⁾

Results

During the study period of 18 months (i.e. 1st January 2014 to 30th June 2015), 1448 patients were given ART. Only 85 patients reported to have ADR related to ART. Out of 85 patients, 58 (68.3%) were female while 27 (31.7%) were male. Female patients had mean age of 33.79±10.38 (years) and mean weight of 46.51±10.11 (Kg). Male patients had mean age of 39.42±11.12 (years) and mean weight of 51.44±9.92 (Kg). Study population had majority of patients in the age group of 21-40 years i.e., 57 (67.1%) (Table 1).

Table 1: Demographic details

Characteristics	n=85 (%)
Gender	
Male	27 (31.7)
Female	58 (68.3)
Age (Years)	
≤ 20	05 (05.9)
21-40	57 (67.1)
41-60	22 (25.9)
≥ 60	01 (01.2)
Weight (Kg)	
< 25	01 (01.2)

25-45	37 (43.5)
45-65	45 (52.9)
> 65	02 (02.4)
Residence	
Rural	24 (28.3)
Urban	61 (71.7)
Education	
Literate	77 (90.6)
Illiterate	08 (09.4)
Occupation	
Employed	33 (38.8)
Unemployed	52 (61.2)
Average monthly income	
≥ 31507	00 (00.0)
15754 – 31506	01 (01.2)
11817 – 15753	03 (03.5)
7878 – 11816	07 (08.2)
4727 – 7877	22 (25.9)
1590 – 4726	45 (52.9)
≤ 1589	07 (08.2)

It was seen that, while 77 (90.6%) patients were literate, only 33 (38.8%) were employed. Majority of patients i.e. 52.9%, belonged to average monthly income group of Rs. 1590 – 4726.

It was also seen that 57 (67.1%) patients were married. Heterosexuality as risk factor of HIV transmission was seen in 75 (88.3%) patients. As far as family members were considered, 50 (58.8%) patients had atleast one member positive (Table 2).

Table 2: Personal and family history

Characteristics	n=85 (%)
Marital status	
Single	07 (08.2)
Married	57 (67.1)
Widowed	18 (21.2)
Divorced	02 (02.4)
Live-in	01 (01.2)
Risk factors for HIV	
Heterosexual	75 (88.3)
Mother to child	06 (07.1)
Blood transfusion	03 (03.5)
Unknown	01 (01.2)
Family members positive for HIV	
1 member positive	46 (54.1)
2 member positive	04 (04.7)
No member positive	35 (41.2)

It was observed that, highest i.e., 57 (62.6%) ADRs were reported from the regimen Zidovudine + Lamivudine + Nevirapine followed by 17 (18.7%) ADRs reported from Tenofovir + Lamivudine + Efavirenze combination regimen (Fig. 2).

Most common types of ADRs were rash (40.6%) and anaemia (26.0%) (Fig. 3). As a consequence of ADRs, 67.0% of regimens were dechallenged (Fig. 1). While, 79 patients had ADRs to one regimen, 6 patients had ADRs to two regimen.

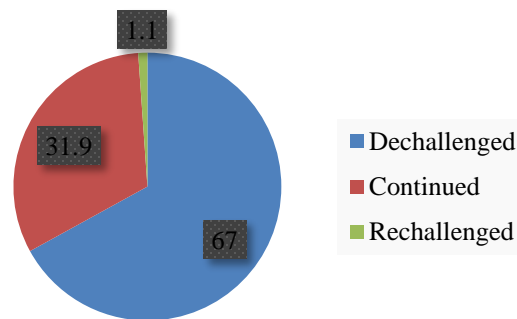


Fig. 1: Regimens

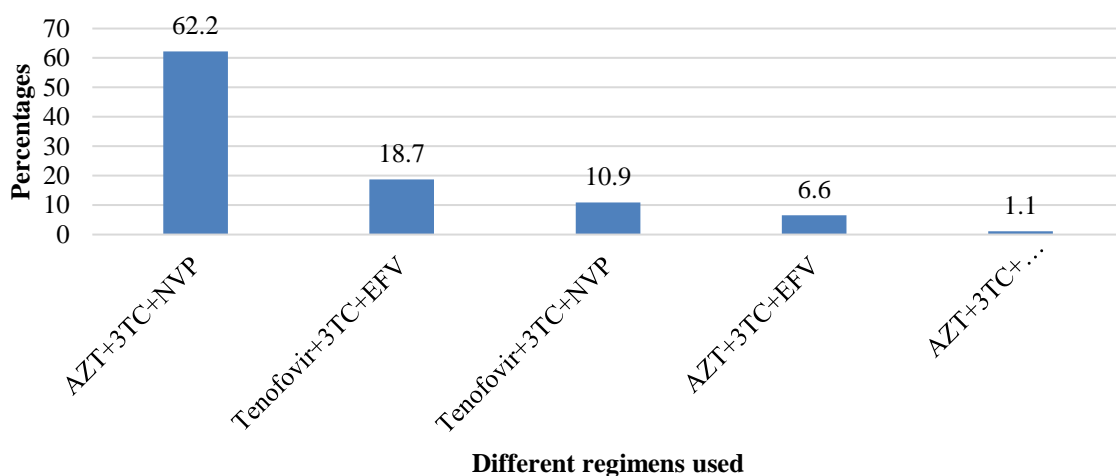


Fig. 2: ADRs to regimens used (%)

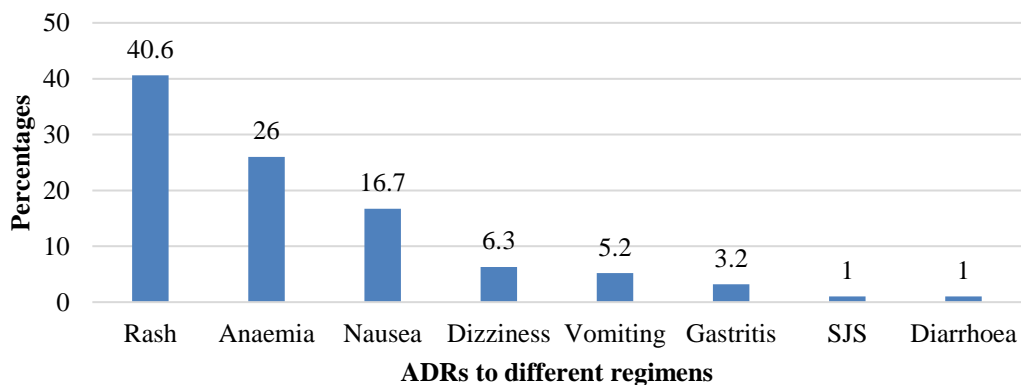


Fig. 3: Percentage of ADRs

According to Naranjo’s causality assessment scale, majority of the ADRs were probable (79.2%) (Table 3). Severity assessment using Modified Hartwig and Siegel’s scale revealed that majority of ADRs were moderate 62 (64.6%) (Table 3). Using Modified Schumock and Thornton preventability assessment scale, 90 (93.8%) ADRs were found to be definitely preventable (Table 3).

Table 3: Assessment of ADRs

Characteristics	n=91 (%)
Causality	
Definite	01 (01.0)
Probable	76 (79.2)
Possible	19 (19.8)
Preventability	
Definitely Preventable	90 (93.8)

Probably Preventable	06 (06.8)
Not Preventable	00 (00.0)
Severity	
Mild	34 (35.4)
Moderate	61 (63.6)
Severe	01 (01.0)

Discussion

Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, reporting and prevention of adverse effects or any other drug-related problem.⁽¹¹⁾ The main emphasis of pharmacovigilance is to detect signals generated as adverse drug events (ADEs) and to establish their causality so as to label them with certainty as adverse drug reactions (ADRs).⁽¹²⁾

In our study, a total of 85 out of 1448 patients had ADRs with an overall prevalence of 5.87% which is much lower than reported by Jha et al.⁽¹³⁾ (16.21%) and Sharma et al.^[14] (71.1%). This could be due to poor monitoring and recording of ADRs.

Our study has shown a higher prevalence of ADRs in females (68.3%) compared to males (31.7%). This was comparable to that found by Agaard et al (60% females and 40% males).⁽¹⁵⁾ This could be due to difference in body weight and body mass index (BMI) between men and women.

Majority of patients i.e., 57 (67.1%) were in the age group of 21-40 years which indicates that adult age group were mostly affected by ADRs. This was comparable to that found by Bhuvana et al.⁽¹⁶⁾ This is because majority of prevalence of HIV is seen in this age group.

Poverty, illiteracy and lack of awareness are playing a major role in the spread of HIV-AIDS. Most of the patients were literate (90.6%), but unemployed (61.2%). Majority of patients, i.e., 52.9% had average monthly income in the range of Rs. 1590 – 4726. The advantage of higher literacy is that, it is easy to educate the patients regarding nature of HIV, available treatment, side effects of available therapy and this can result in higher compliance and also higher rate of employment which can make financial aspect better. Majority of patients were married (67.1%).

Sero-conversion in spouse was reported in 54.1%, which was higher than that found by Miranda Pegu et al.⁽¹⁷⁾ (36%). Heterosexuality (88.3%) was the most common mode of HIV transmission which was similar to findings reported by Talukdar et al.⁽¹⁸⁾

Out of 85 patients, 6 patients had ADRs to two regimen, i.e., total 96 ADRs. In this study, zidovudine + lamivudine + nevirapine was the most common regimen which caused ADRs. This finding was similar to Bhuvana KB et al.⁽¹⁶⁾

In this study, rash (40.6%) followed by anaemia (26.0%) were found to be the most common types of ADRs. This finding was similar to Sharma et al.⁽¹⁹⁾ with rash and anaemia as 44.4% and 32.2%, respectively.

A study by Sivadasan et al.⁽²⁰⁾ highlighted that adverse effects of various drugs of the ART regimens were one of the main causes for changes in regimen used. Similarly, in this study, 67% of the regimens were changed (i.e., dechallenged) due to ADRs.

Rash (40.6%) was seen with the regimens containing mainly nevirapine (76.9%) and efavirenz (23.1%) to certain extent. It was managed conservatively, nevirapine was substituted with efavirenz and efavirenz was substituted with atazanavir + ritonavir. Similarly, the study conducted by Martínez et al.⁽²¹⁾ had also shown high prevalence of rash by use of nevirapine. Steven Johnson Syndrome (SJS) is the severe emergency medical condition which is seen with use of nevirapine. In our study, we have found 1 cases of SJS due to nevirapine where the patients were the patient developed diffuse, exfoliating exanthema with generalized bulbous eruptions all over the body.

Anemia (26.0%) was seen with regimen containing zidovudine and rise in the haemoglobin level was observed on discontinuing zidovudine, and this was similar to studies done by Curkendall et al.⁽²²⁾ and Huffam et al.⁽²³⁾ Regimen containing zidovudine was substituted with tenofovir containing regimen in patients who developed anemia.

Nausea (16.7%) and vomiting (5.2%) was seen with regimen containing mainly zidovudine and tenofovir to certain extent. While study conducted by Akshaya Srikanth et al.⁽²⁴⁾ showed reverse trend (vomiting (5.71%) and nausea (0.95%)).

Neurological ADRs were predominant in patients on efavirenz and included dizziness (6.3%). This finding was less than study conducted by Kumar et al. (12.69%).⁽²⁴⁾

In our study, use of nevirapine was associated with gastritis (3.2%). This finding was less than study conducted by Lihite et al. (13.1%).⁽²⁵⁾

Causality assessment of ADRs by Naranjo's scale revealed that most of the ADRs were probable (79.2%) followed by possible (19.8%) and lastly definite (1%). These results are similar to the study conducted by Rajesh et al. were majority of (63.5%) ADRs were probable.⁽²⁶⁾ Re-challenge was attempted in one case, which violated ethics in patient care.

Severity assessment of ADRs by Modified Hartwig and Siegel's Scale revealed that most of the ADRs were of moderate intensity (63.6%) followed by mild intensity (35.4%) and lastly severe intensity (1%). These results are similar to the study conducted by S.R. Anwikar et al.⁽²⁷⁾ were majority of (77.19%) ADRs were of moderate intensity.

Preventability assessment of ADRs by Modified Schumock and Thornton's Scale revealed that most of the ADRs were definitely preventable (93.8%) followed by probably preventable (06.2%) and none of the ADRs were not preventable. These results are similar to the study conducted by Kumar et al.⁽²⁴⁾ were majority of (77.19%) ADRs were of moderate intensity.

Limitations

Since the study was conducted in only one nodal ART centre of Government hospital in Central India, it did not include the actual number of HIV-AIDS infected patients who were receiving ART and developed ADRs. Also, as sample size was very small, we could not show any statistical significance among different parameters and arrive at any definite conclusion.

Conclusion

Majority of ADRs in our study can be minimized by changing the regimen and many are self-limiting. Though, ART is capable of halting and reversing the number of AIDS-related deaths, it is also associated with ADRs involving many organ systems. Identification of risk factors like age, gender and regimen used is important to optimize the first choice of ART regimen before starting therapy and to avoid complications due to ART. AZT+3TC+NVP/EFV regimen is a marker of ADRs. HIV positive patients who are in the age group of 21-40 years and literate needs intensive counselling regarding side effects of available ART therapy and this can lead to higher compliance. And finally, prevalence of ART induced ADRs is significantly less in our center, which requires prompt monitoring and recording of ADRs.

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Conflict of interest: None.

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

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