ORIGINAL ARTICLE

Incidence of adverse drug reactions in human immune deficiency virus-positive patients using highly active antiretroviral therapy

B. Akshaya Srikanth,
S. Chandra Babu[1],
Harlokesh Narayan Yadav[2],
Sunil Kumar Jain[3]

Department of Pharmacy Practice, P.R.R.M. College of Pharmacy, [1]Department of Medicine, Rajiv Gandhi Institute of Medical Sciences (RIMS), Kadapa, Andhra Pradesh, [2]Department of Pharmacology, Bharat Institute of Technology, Meerut, U.P, [3]Chief Pharmacist, AIIMS, New Delhi, India

J. Adv. Pharm. Tech. Res.

ABSTRACT

To estimate the incidence of adverse drug reactions (ADRs) in Human immune deficiency virus (HIV) patients on highly active antiretroviral therapy (HAART). To identify the risk factors associated with ADRs in HIV patients. To analyze reported ADRs based on various parameters like causality, severity, predictability, and preventability. Retrospective case-control study. An 18-month retrospective case-control study of 208 patients newly registered in ART center, RIMS hospital, Kadapa, were intensively monitored for ADRs to HAART. Predictability was calculated based on the history of previous exposure to drug. Multivariate logistic regressions were used to identify the risk factors for ADRs. Data were analyzed using the chi-square test for estimating the correlation between ADRs and different variables. All statistical calculations were performed using EpiInfo version 3.5.3. Monitoring of 208 retrospective patients by active Pharmacovigilance identified 105 ADRs that were identified in 71 patients. Skin rash and anemia were the most commonly observed ADRs. The organ system commonly affected by ADR was skin and appendages (31.57%). The ADRs that were moderate were 90.14% of cases. The incidence of ADRs (53.52%) was higher with Zidovudine + Lamivudine + Nevirapine combination. CD4 cell count less than <250 cells/μl were 80.28%, male gender were observed to be the risk factors for ADRs. Our study finding showed that there is a need of active pharmaceutical care with intensive monitoring for ADRs in Indian HIV-positive patients who are illiterate, of male and female gender, with CD4 count ≤250 cells/mm^3 with comorbid conditions.

Key words: Adverse drug reactions, antiretroviral therapy, HIV/AIDS, India, pharmacovigilance

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is caused by Human immune deficiency virus (HIV), a virus that is transmitted from person to person through sexual fluids, blood, and breast milk. Majority of HIV infections are transmitted through sex between men and women, and include injecting drug users, sex workers, and men who have sex with men.[1]

An estimated 33.3 million people are living with HIV and around 3 million people have accessed to the highly active antiretroviral therapy (HAART) worldwide as on 2009.[2]

Today, around 4.87 million people are living with HIV in South, East, and South-east Asia. In India, an estimated 0.1% of adults aged 15 to 49 years are living with HIV; however, with a population of around one billion, this actually equates to 2.3 million adults living with HIV in India.[2,3]

The introduction of HAART in 1996 with three antiretroviral (ARV) drugs primarily in the combination of one Protease

Address for correspondence:
Dr. B. Akshaya Srikanth,
Pharm. D Intern, Department of Pharmacy Practice, P.R.R.M. College of Pharmacy, Kadapa, Andhra Pradesh-5160003, India.
E-mail: akshaypharmd@gmail.com

Access this article online

Quick Response Code:

Website: www.japtr.org

DOI: 10.4103/2231-4040.93557

Inhibitor (PI) and two Nucleoside reverse transcriptase inhibitors (NRTIs) has led to significant reduction in AIDS-related morbidity and mortality.[4]

As now with the initial HAART regimen should contain a Non-NRTI (either nevirapine [NVP] or efavirenz [EFV]) plus two NRTIs (lamivudine [3TC] or emtricitabine [FTC]), and other zidovudine (AZT) or tenofovir disoproxil fumarate (TDF).[5] As per the world health organization (WHO) recommendations, the HIV-positive patients with CD4 counts ≤350 cells/mm^3 and WHO clinical staging of HIV disease in adults stage 1 and 2.[6] Although there are benefits associated with earlier initiation of HAART, there are also potential limitations like long-term toxicity and development of ARV resistance. As the HAART improves the quality of life among symptomatic patients, it is also associated with reduced quality of life in some patients.

Treatment adherence is the key to viral suppression and should stress prior to initiation of therapy during follow-up visits or monitoring the patient.[7]

One study found that an increased incidence of cardiovascular diseases is associated with cumulative exposure to some drugs within the NRTI and PI classes.[8]

Adverse effects have been reported with all ARV drugs and are among the most common reasons for switching or discontinuing therapy as well as for medication nonadherence.[9]

Several factors predispose individuals to adverse effects of ARV medications, like women seems to have higher propensity of developing Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine.[10-12]

The HAART is the only treatment option for treating the HIV-positive virus patients for improving the immune system by increasing the number of CD4 cells essential to protect body from infections and cancers.[13]

The study was conducted to assess the incidence, prevalence, severity pattern, predictability, preventability of adverse drug reactions (ADRs) to HAART, and to identify the risk factors for ADRs in HIV-positive patients receiving HAART.

MATERIALS AND METHODS

This was a retrospective study conducted at the Anti-retroviral department, Rajiv Gandhi Institute of Medical Sciences, Kadapa, India. The study was approved by Institutional Ethical Committee of Rajiv Gandhi Institute of Medical Sciences (RIMS), Kadapa (Rc. No. Spl/Academic/E3-A/2011-12). HIV-positive patients with fixed dose of HAART were included.

Patients between January 2010 and May 2011 were included for the study.

All the patients above 16 years newly registered HIV patients on HAART therapy of either sex were included.

Patients taking anti-tubercular treatment, opportunistic infections, second-line drugs like TDF/lamivudine (3TC) + atazanavir/low-dose ritonavir (ATV/R), and pregnant women were excluded from the study.

Demographic details, occupation details, education, CD4 cell count, weight and hemoglobin (Hb), available laboratory data, drugs used, and susceptible ADRs observed were recorded in a specially designed data collection form.

The following four types of HAART regimens were used:
1. Stavudine, Lamivudine, and Nevirapine (21.15%)
2. Zidovudine, Lamivudine, and Nevirapine (41.34)
3. Stavudine, Lamivudine, and Efavirenz (12.5%)
4. Zidovudine, Lamivudine, and Efavirenz (25%)

The prevalence was calculated by considering the ratio of number of patients with ADRs and total number of patients involved in the study.

Incidence rate was calculated by considering the ratio of ADRs and the exposure patients.

Data were analyzed using the chi-square test for estimating the correlation between ADRs and different variables.

Risk factors for the ADRs were determined at a *P* value <0.05 by investigating the effects of gender, age, CD4 count, weight, and concomitant drugs.

All statistical calculations were performed using EpiInfo version 3.5.3.

A *P* value of <0.05 was considered as statistically significant.

RESULTS

A total of 208 retrospective patients with newly registered for the HAART (121 males [58.17%] and 87 female [41.82%]) were admitted during the period of January 2010 to May 2011 to the RIMS hospital.

Of 208 retrospective patients, number of patients with ADRs were 71 (40 males [56.33%] and 31 female [43.66%]).

Number of ADRs to HAART during the 18-month study period was 105 (63 males [60%] and 42 females [40%]).

But, ADRs in patients who were 50 years and above (50 [7.04%]) were also included.

The prevalence of ADRs in our study was higher in female population (41.82% [31/87]) compared with males (33.05% [40/121]).

The incidence rates of ADRs were higher in age group 31 to 40 years with 29/71 (40.84%) and majority of ADRs observed in males (18/71 [25.35%]) to HAART was found to be 34.13% [Table 1].

The majority of ADRs observed in males (60%) under the age group 31 to 40 years (40.84%) of patients (18 [25.35%]) were observed and Regression analysis identified, CD4 count <250 cells/mm^3 [Table 2].

In 71 patients 105 suspected ADRs 46 (64.78%) developed one ADR, 16 (22.8%) developed two ADRs, and 9 (12.67%) developed three ADRs [Figure 1].

The organ system affected in majority of ADRs was skin and appendages (31.57%) followed by central peripheral nervous system (18.07%), red blood cells (16.19%), gastrointestinal (13.56%), liver and biliary disorder (6.85%), and psychiatry (3.45%) were the least observed [Table 3].

Almost all the ADRs were mild to moderate, the suspected drugs were withdrawn in 90.14% (64/71) of ADRs and symptomatic treatment was continued to remaining cases (9.85% [7/71]). Higher incidence rate was observed with Zidovudine + Lamivudine + Nevirapine combination

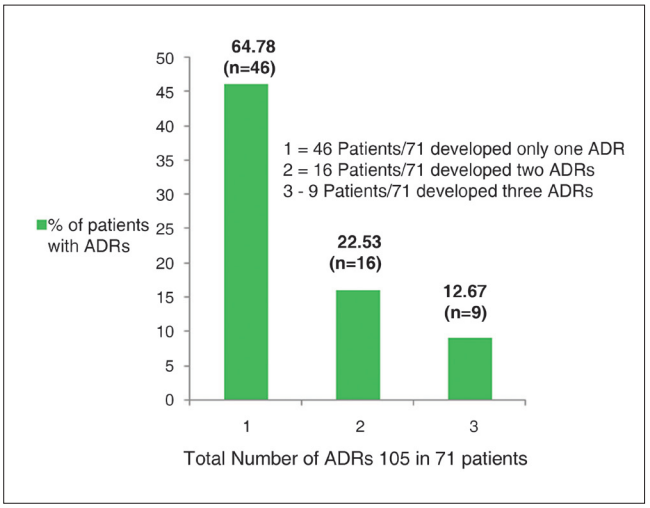

Figure 1: Number of ADRs reported vs % of patients

Table 1: Demographic details of patients in Kadapa area

Characteristic	No. of patients *n*=208 (%)	No. of ADRs for HAART *n*=71 (%)	No. of ADRs observed/ total no of patients	Incidence (% age)	Overall incidence of ADRs (%)
Gender					50.48
Male	121 (58.17)	40 (56.33)	63/121	52.06	
Female	87 (41.82)	31 (43.66)	42/87	48.27	

Table 2: Age of patients

Characteristic	No. of patients *n*=208 (%)	No. of ADRs for HAART *n*=71 (%)	No. of ADRs observed/total no of patients	Incidence (%)	Overall incidence of ADRs (%)
Age (years)					50.48
17-30	64 (30.76)	18 (25.35)	24/64	37.5	
31-40	81 (38.94)	29 (40.84)	43/81	53.08	
41-50	45 (21.63)	19 (26.76)	31/45	68.88	
51-60	15 (7.21)	5 (7.04)	7/15	46.66	
>60	3 (1.44)	0 (0.00)	0/3	0	
CD4 count in ADR patients		**Total number of patients *n*=71 (%)**			
CD4 count (Cells/mm^3) cases	**Male (%)**	**Female**	**Total**	**N (%)**	***P* value**
≤250	35 (49.29)	25 (35.21)	60	84.51	0.9218
>250	6 (8.45)	5 (7.04)	11	15.49	
CD4 count in without ADR patients: Control		**Total number of patients *n*=137 (%)**			
CD4 count (Cells/mm^3)	**Male (%)**	**Female**	**Total**	**N (%)**	***P* value**
≤250	66 (44.17)	43 (31.38)	109	79.56	0.6494
>250	15 (10.94)	13 (9.48)	28	20.43	
CD4 count in ADR and Non-ADR patients: Case vs Control		**Total number of patients *n*=208 (%)**			
CD4 count (Cells/mm^3)	**Male**	**Female**	**Total**	**N (%)**	***P* value**
≤250	101 (48.55)	68 (32.69)	167	80.28	0.6199
>250	21 (10.09)	18 (8.65)	39	18.75	

(38/105 [53.52%]) and incidence of ADRs was low in Stavudine + Lamivudine + Efavirenz (19/105 [18.09%]) [Table 4].

The commonly observed ADRs were skin rash (30), followed by anemia (17), poly neuritis (11), fever, and vomiting (6) [Table 5].

Nevirapine use was observed as a risk factor for ADRs like skin rash and hepatitis. Zidovudine use was identified as a risk factor for ADRs like anemia and vomiting, while Stavudine use was the risk factor for the peripheral neuropathy.

DISCUSSION

This is the first retrospective study on the incidence of ADRs in HIV-positive patients using HAART in HIV-positive patients. The study observed the significant ADRs associated with the use of HAART in the local population of Kadapa, India. In our study, majority of ADRs to HAART was observed under the age group 31 to 40 years. This may be due to large number of new HIV-positive patients treating with HAART at our hospital. A finding of ADRs observed in adults was similar to another study.[14,15] However, other study[16] has reported large percentage of ADRs in geriatric and pediatric populations.

Table 3: Organ wise system affected due to adrs to haart (system organ class code WHO-ART)

	% of ADRs
Skin and appendages (0100)	31.57
Vascular (1040)	
Central peripheral nervous system (0410)	18.07
Gastro intestinal (0600)	13.56
Red blood cells (1200)	16.19
White cell and res (1220)	
Platelets, bleeding and clotting (1230)	
Urinary system disorder (1300)	
Liver and billary disorder (0700)	6.85
Psychiatry (0500)	3.45
Metabolic and nutrition (0800)	
Body as a whole (1810)	1.95
Resistance mechanism disorders (1830)	8.71

During the study, 64.78% of patients showed at least one ADR and switched to another drug regimen, which was done in 90% of the patients. Skin rash and weakness, anorexia complaints were the most prevalent reported ADRs in our study; most ADRs were moderate and need just symptomatic treatment in few patients. Skin rash adverse effects were reported more with Nevirapine-containing HAART regimen. Anemia occurred in patients who received zidovudine-containing regimens who were graded according to the National aids control organization (NACO) criteria. In majority of cases, Grade I anemia (Hb, 8.0-9.5 g/dl) was observed with Zidovudine.[17]

Skin rash developed in 28.57% (30/105) people taking Nevirapine. These side effects are much more common in males than females in our study. The patients frequently complain about the skin rash being uncomfortable. Mild rash occurs with no other related symptoms and resolves over days or weeks. Moderate rash may be accompanied by systemic symptoms (e.g., fever, LFT abnormalities, and myalgias). Life-threatening rashes like Stevens-Johnson syndrome associated with pain, mucous membrane involvement, fever, LFT changes, and myalgias can be fatal.

In our study, Hepatitis (2.85% [3/105]), jaundice (1.90 [2/105]), and hyperbilirubinemia (1.90 [2/105]) were also associated with nevirapine and efavirenz and the elevated levels of bile, ALT, AST, and bilirubin levels according to the NACO grades of clinical and laboratory toxicities.[17]

Hematological abnormalities (16.19% [17/105]) were more with zidovudine-containing HAART regimen; an improvement in Hb level was observed on discontinuation of zidovudine, similar to the finding reported by Koduri and Parekh.[18] In our study, patients initiated on a zidovudine-containing regimen only if they had the Hb levels more than 10.5 g/dl at baseline, thereby avoiding the occurrence of zidovudine-induced anemia. However, we observed a highly significant association between the zidovudine and anemia, which is similar to other studies.[19,20]

Table 4: NACO HAART regimen implicated in ADRs (*n*=71) doses

	Number of prescriptions *n*=71 (%)	Number of ADRs *n*=105 (%)	Incidence of ADRs *n*=105 (%)	*P* value
Regimen I				
Zidovudine + Lamivudine + Nevirapine	33 (46.47)	38 (53.52)	36.19	
Regimem I (a)				
Stavudine + Lamivudine + Nevirapine	14 (19.71)	28 (39.43)	26.66	0.4166
Regimen II				
Zidovudine + Lamivudine + Efavirenz	15 (21.12)	20 (28.16)	19.04	
Regimen II (a)				
Stavudine + Lamivudine + Efavirenz	9 (12.67)	19 (26.76)	18.09	

NACO: National AIDS control organization, WHO-ART: World health organization –Adverse reaction terminology, HAART: Highly active antiretroviral therapy

Table 5: Adverse drug reactions to antiretroviral drugs in HIV patients

Adverse drug reaction	Number of ADRs *n*=105 (%)
Skin rash	30 (28.57)
Anaemia (Hb in g/dl)	17 (16.47)
Grade 1 (9.5-8.0 g/dl)	7 (3.08)
Grade 2 (7.9-7.0g/dl)	6 (5.71)
Grade 3 (6.9-6.5g/dl)	1 (0.95)
Grade 4 (<6.5g/dl)	3 (2.85)
Poly neuritis	11 (10.47)
Vomiting	6 (5.71)
Fever	6 (5.71)
Headache	4 (3.8)
Drowsiness	4 (3.8)
Immune reconstitution inflammatory syndrome	3 (2.85)
Hepatitis	3 (2.85)
Diarrhea	3 (2.85)
Jaundice	3 (2.85)
Hyper bilirubunemia	2 (1.9)
Fatigue	2 (1.9)
Dyspepsia	2 (1.9)
Depression	2 (1.9)
Acid peptic disorder	2 (1.9)
Alopecia	1 (0.95)
Nausea	1 (0.95)
Discoloration of nails	1 (0.95)
Insomnia	1 (0.95)
Hyper pigmentation	1 (0.95)
Dermatitis	1 (0.95)

Peripheral neuropathy was observed in patients who were on stavudine-containing regimen for more than 4 months. In 10.47% (11/105) of these cases, stavudine was discontinued and the patient recovered. However, a few patients who took zidovudine therapy also suffered with peripheral neuropathy, followed by fever (5.71% [6/105]) and also finding in our study shows stavudine as a risk factor for the peripheral neuropathy, which is also suggested from Scarsella *et al*.[21]

Vomiting (5.71 [6/105]) was a common ADR, followed by nausea (0.95% [1/105]), diarrhea (2.85% [3/105]), dyspepsia (1.90% [2/105]), fatigue (1.90 [2/105]), hyper pigmentation of skin (0.95% [1/105]), and discoloration of nails (1.90% [2/105]) that were observed among patients who were on regimens containing zidovudine. Majority of the patients experienced vomiting after ingestion of the drug. Patients receiving a zidovudine-containing regimen had the greater risk of vomiting, which is similar to that observed in an Iranian study.[22]

The occurrence of depression headache (3.80% [3/105]), drowsiness (3.80% [3/105]), depression (1.90 [2/105]), alopecia (0.95% [1/105]), and insomnia (0.95% [1/105]) was highly associated with efavirenz therapy. The occurrence of this ADR can be minimized by administering the efavirenz once a day at night. Our study observations were similar to the study by Fumaz *et al*.[23]

In our study, patients complained ADRs of dermatitis (0.95% [1/105]), GI reflex disorder (1.90% [2/105]); these ADRs with unknown reason and immune reconstitution inflammatory syndrome (IRIS) was observed within the first six months of HAART. In three patients (3.80% [3/105]) IRIS manifested as TB. Our study findings are similar to a South African study wherein most of IRIS cases (41%) manifested as TB.[24]

The majority of the ADRs were predictable as they were common (incidence ≥1/100) and very common incidence ≥1/10.[25]

The preventive measures for ADRs were prescribed and administered to patients: like common instructions were give to avoid ADRs by providing medication counseling to each patient. The finding of study showed that the most common causes of ADRs to HAART in these patients were found to be cutaneous, like skin rash, dermatitis, hyperpigmentation, and discoloration of nails with nevirapine and efavirenz. Hematological ADRs like anemia with Zidovudine and polyneuritis ADR was observed in patients using Stavudine therapy.

CONCLUSION

This is the first active Pharmacovigilance study that was designed to evaluate the incidence of ARV therapy-induced ADRs in Indian HIV-positive patients.

HAART with zidovudine + lamivudine + nevirapine (53/105), zidovudine + lamivudine + efavirenz (37/105), and stavudine + lamivudine + nevirapine (30/105) causing ADRs are self limiting and few ADRs can be minimized by switching the regimen.

ARV therapy is effective for HIV treatment but also increasingly complex. The many adverse effects of therapy may cause symptoms affecting a variety of organ systems. Although current ARV regimens are potent from an ARV perspective, they often fail because of nonadherence. To optimize adherence, treating physicians must focus on early detection and prevention of ADRs, when possible and distinguishing those that are self-limited from those that are potentially serious. Physicians must remain aware of new and developing syndromes associated with ARV use. In the new era of HAART, physicians must be trained to identify and manage the toxicities associated with HAART as well.

Our study finding showed that there is a need of active pharmaceutical care with intensive monitoring for ADRs in Indian HIV-positive patients who are illiterate, of male and female gender, with CD4 count ≤250 cells/mm^3 with comorbid conditions.

ACKNOWLEDGEMENTS

The authors thank staff of Medicine and administrative staff of RIMS Medical College, Kadapa, for their support and encouragement and Special thanks to Pharmacy Practice department for their continuous support.

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How to cite this article: 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 Tech Res 2012;3:62-7.

Source of Support: Nil, **Conflict of Interest:** Nil.