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Adverse Drug Reactions Related To Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus Positive Patients - A Prospective Study

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Abstract **Original Research Article**

Background: ART has proved to be a boon to people living with HIV by reducing disease progression, decreasing viral load and increasing their life span. However, these ART drugs are not devoid of adverse effects. Though the benefits of ART are for all to see, we cannot ignore the multiple adverse events that have been reported with their use. The present study was thus designed to study the incidence and prevalence of ADRs and its profile of occurrence to various antiretroviral therapy (ART) regimens in a tertiary care hospital. ***Materials and Methods:*** A prospective, observational clinical study was carried out in tertiary care institute. A total of 303 patients on various ART regimens were studied for suspected ADRs over 18 months. Demographic profile, Clinical history, Adverse event history, medication history, and other relevant details were recorded. Data was analysed to study the incidence, prevalence and predictive factors of adverse drug reactions related to antiretroviral therapy. ***Results:*** The incidence and prevalence of adverse drug reactions was found to be 19.5% and 31.4%, respectively. 109 adverse drug reactions were reported in 95 patients. Females (58) had more ADRs than males (37). Maximum number of patients were on Zidovudine+Lamivudine+Nevirapine regimen (158 patients). Anemia (10.6%) was the commonest adverse drug reaction in our study, followed by neuropsychiatric disturbances (6.9%) and rash (6.3%). Adverse drug reaction was the commonest reason for change of drug regimen in our study population (74.5%).20.3% cases with CD4 count 100-250 had Anemia which was significantly more as compared to 6.8% and 10.6% cases with CD4 count 251-500 and >500. 13.6% cases with CD4 count 100-250 had Nephrotoxicity which was significantly more as compared to 1.5% and 1.0% cases with CD4 count 251-500 and >500. ***Conclusion:*** High incidence and prevalence of ADR in patients on HAART suggest need of intensive monitoring for ADRs in such patients. Low CD4 count, Female gender and associated comorbidities found to have risk factors for development of ADR.

Keywords: Antiretroviral Therapy, ART drugs, Immunodeficiency Virus.

INTRODUCTION

India has the third highest number of estimated people living with HIV in the world. The total number of people living with HIV (PLHIV) in India is estimated at 21.17 lakhs (17.11 lakhs–26.49 lakhs) in 2015 [1].

With the availability of new antiretroviral drugs, there has been a decline in morbidity and mortality due to acquired immunodeficiency syndrome [2].

The development of multi-drug combination therapy for treatment of HIV disease is considered one of the great success stories of modern medicine [3]. In a period of approximately ten years, the death rate from HIV disease was reduced by 50 to 80% and changed from a nearly universally fatal and catastrophic illness to what is now often a manageable chronic illness.

ART has proved to be a boon to people living with HIV, in reducing disease progression, decreasing viral load and increasing their life span. However, these ART drugs are not devoid of adverse effects.

Though the benefits of ART are for all to see, we cannot ignore the multiple adverse events that have been reported with their use.

Adverse effects are among the most common reasons for switching or discontinuing therapy as well as for medication nonadherence.

The ART drugs affect all systems from gastrointestinal to cardiac and cutaneous to central nervous system [4].

With the increase in average age of the HIV population, we are more likely to deal with more adverse events in the future.

We have done a study, to estimate the prevalence and incidence of adverse drug reactions and to evaluate independent clinical and laboratory predictive factors of adverse drug reactions to Highly Active Antiretroviral Therapy (HAART).

Adverse drug reactions (ADRs) are still largely underreported in our country. It was our hope to provide evidence-based information to medical professionals to sensitize and encourage them to report ADRs.

MATERIAL AND METHODS

A prospective, observational study was conducted to determine Adverse Drug Reactions Related to Highly Active Antiretroviral Therapy in Human Immunodeficiency Virus Positive Patients attending the ART and Medical Outpatient department as well as admitted patients in a tertiary care hospital over a period of 18 months.

Around 303 patients were serially recruited in the study after taking written valid consent. Institutional ethics approval was taken and confidentiality of information was duly maintained and basic principles of ethics in clinical research were strictly followed.

Patients demographic profile, ART registration number, date of initiating ART, duration of treatment, current drug regimen and other relevant details were noted.

Clinical history for symptoms like fatigue, jaundice, rash, generalized weakness, breathlessness, hyperpigmentation, oliguria was asked and their duration noted. History of medications and complications was taken. Clinical examination like pulse, B.P., general examination, and evidence of rash, pallor, icterus, lymphadenopathy, pedal oedema were sought for. A thorough systemic examination was done.

Relevant investigations like a Complete blood count, Peripheral smear, liver and renal function tests, lipid profile, CD4 counts, serum amylase, viral markers, urine routine and radiological investigations like Chest X ray, Ultrasonography of abdomen, etc. were done.

Patients were observed and followed up for development of any adverse effects of HAART. Data was analysed to study the incidence, prevalence and predictive factors of adverse drug reactions related to antiretroviral therapy.

In this study all statistical analysis was perform by using 10.0 version of statistical software SPSS.

Data analysis was done by independent and neutral statistician using tests of statistical significance like Chi square test and student t test.

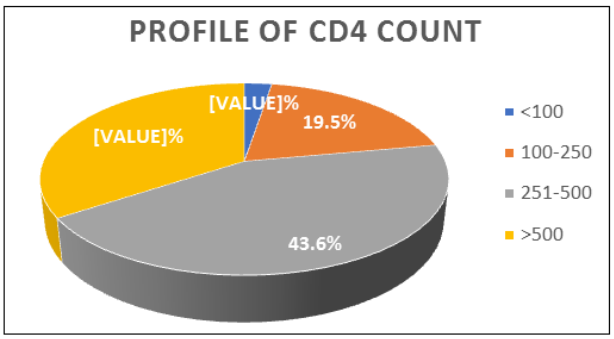
All p-values were reported based on two-sided significance test and all the statistical tests was interpreted at 5% level of significance level.

RESULTS

Total 303 patients were included in our study, 52.5% of cases were male and 47.5% of cases were female. Mean age of our study group was 36.7yrs.

In our study 52.1% (158/303) cases were on ZLN regimen and 42.9% (130/158) cases on TLE regimen and rest others were on SLN (7/303), ZLE(7/303),TLN(3/303), ALN(1/303).

As shown in Graph-1, 43.6% of the cases had 251-500 CD4 counts followed by 34.3% cases had >500 CD4 counts and 19.5% cases had 100-250 CD4 counts.



Graph-1: Profile of Patients with CD4 Counts

In our study, out of 303 patients, 95 patients (58 female and 37 male) had 109 adverse drug reactions, the incidence and prevalence of ADR was found to be 19.5% and 31.4%, respectively.

As per Table-1, most common ADR reported in our study is anemia (10.6%) followed by neuropsychiatric disturbances (6.9%) and rash (6.3%).

Table-1: Profile of ADR in patients HIV

ADR	No.ofCases (N=303)	Percentage (%)
Anemia	32	**10.6**
Neuropsychiatric disturbances	21	06.9
Rash	19	06.3
Nephrotoxicity	11	03.6
Dyslipidemia	08	02.6
Hepatitis	06	01.9
Gastritis	04	01.3
Hyperpigmentation	02	00.7
Psychosis	01	00.3
Gynaecomastia	01	00.3
Lactic Acidosis	01	00.3
Lipoatrophy	01	00.3
Lipodystrophy	01	00.3
Pancreatitis	01	00.3

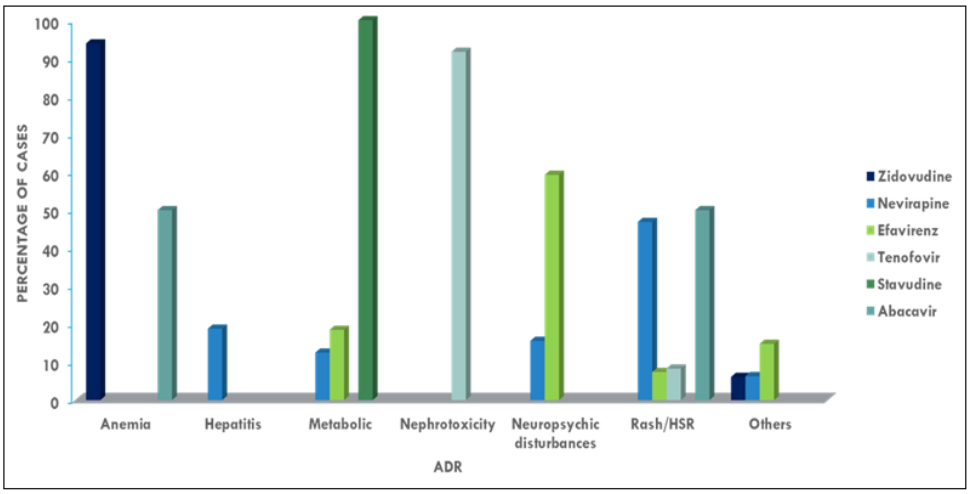
Out of 109 patients 80(73.4%) needed change of regimen due to ADR and 10 required with hold of treatment for some duration, while 18(16.5%) patients were kept under observation without change of regimen for resolution of ADR.

Graph-2 shows that, 93.9% of cases who developed ADR while on Zidovudine had anemia which was significantly more as compared to 50.0% of cases who developed ADR while on Abacavir drug.

12.5% cases who developed ADR while on Nevirapine drug had metabolic disorders which was significantly less as compared to 100.0% and 18.5% cases who developed ADR while on Stavudine and Efavirenz drugs, respectively.

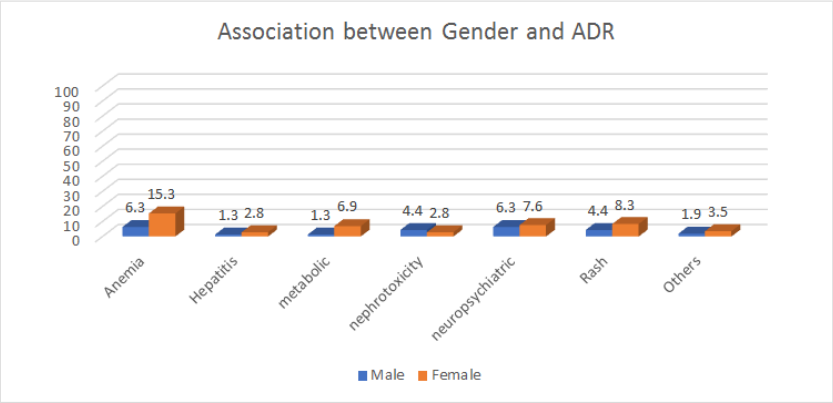
59.3% cases who developed ADR while on Efavirenz drug had Neuropsychiatric disturbances which was significantly more as compared to 15.6% cases who developed ADR while on Nevirapine drug.

46.9% cases who developed ADR while on Nevirapine drug had Rash which was significantly more as compared to 7.4%, 8.3%, and 50.0% cases who developed ADR while on Efavirenz, Tenofovir and Abacavir drugs, respectively.



Graph-2: Association drugs with ADR

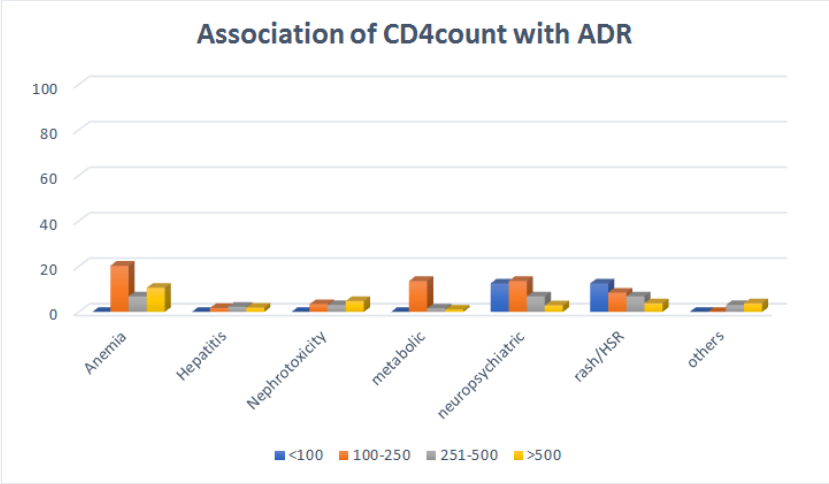
Out of 144 patients 22 (15.3%) of female cases had Anemia which was significantly more as compared to 10 out of 159 (6.3%) of male cases. Also 10 out of 144 (6.9%) of female cases had metabolic disorders which was significantly more as compared to 2 out 159 (1.3%) of male cases.



Graph-3: Association of Gender and ADR

Similarly 20.3% (12/59) cases with CD4 count 100-250 had Anemia which was significantly more as compared to 6.8%(09/132) and 10.6% (11/104) cases with CD4 count 251-500 and >500 respectively.

We also found that 13.6% (8/59) cases with CD4 count 100-250 had Nephrotoxicity which was significantly more as compared to 1.5% (2/139)and 1.0% (1/104) cases with CD4 count 251-500 and >500 respectively.



Graph-4 Association of CD4 count with ADR

DISCUSSION

Recent increases in access to highly active antiretroviral therapy (HAART) have made the management of drug toxicities an increasingly crucial component of human immunodeficiency virus (HIV) care in developing countries.

However, prolonged treatment with combination regimens can be difficult to sustain because of problems with adherence and toxic effects. All antiretroviral drugs can have both short-term and long-term adverse events. The risk of specific side effects varies from drug to drug, from drug class to drug class, and from patient to patient.

The spectrum of adverse effects associated with HAART may vary between developed and developing countries for several reasons as below-

- Economic constraints limit the repertoire of accessible antiretroviral medications.
- Prohibitory laboratory monitoring costs.
- Comorbid conditions and usage of alterative medications (herbal, ayurvedic) that are more prevalent in resource-limited regions, such as anemia and malnutrition etc.
- Host genetics may be associated with drug toxicities [5].

In our study, out of 303 patients, 95 patients (58 female and 37 male) had 109 adverse drug reactions.

In our study, (Table-1) 10.6% cases had Anemia followed by 6.9% cases had Neuropsychiatric disturbances, 6.3% cases had Rash, 3.6% had Nephrotoxicity and 2.6% had Dyslipidemia. In the study by Modayil *et al*., [6], Anaemia and vomiting were the most commonly observed ADRs. Also, skin rash and anemia were the most commonly observed ADRs in a study by Srikanth *et al*., [7].

In this study 32 patients had anemia. Of which 31 patients (96.9%) were on Zidovudine. (Graph-2) The role of zidovudine based regimen causing myelosuppression is now widely accepted. The prevalence of anemia in our study was 10.6% (Table-1). The epidemiological studies from various parts of the world shows that the prevalence of Zidovudine induced anaemia vary widely with 5.42- 9.62% [8]. From a study in a ART centre in Banaras, India, 16.2% patients developed zidovudine induced anaemia [9].

The prevalence of neuropsychiatric disturbances in our study was 6.9% (21/109), second only to anemia (Graph-2). Out of 21 patients 16 were on Efavirenz and 5 were on Nevirapine. This increasing prevalence maybe in part due to Efavirenz now being a part of first line ART in India. Also in patients with TB treatment to needs Efavirenz based regimen.

In pivotal clinical trials, more than 50% of patients taking efavirenz experienced some CNS effects, although few patients discontinued treatment as a result [10]. Thus, in our study Efavirenz was significantly associated ($p<0.05$) with neuropsychiatric disturbances and should be cautiously used in patients with a past history of psychological/ psychiatric disorders.

In our study, 11 out of 11 patients (100.0%) cases who developed nephrotoxicity were on tenofovir. The prevalence of nephrotoxicity in the form of acute kidney injury was 2.6% in our study (Table-1). Similar results were found in other studies as well [11, 12].

In our study, 6 out of 6 patients (100%) who developed hepatitis were on Nevirapine. The prevalence in our study was 1.9%. In a study by Martinez *et al.*, Hepatotoxicity developed in 12.5% of the patients [13], which was more as compared to what we found in our study. This correlation has been further found in several other cohort studies [14, 15].

In our study, 12.5% cases who developed ADR while on Nevirapine drug had metabolic disorders (included lactic acidosis, dyslipidemia, lipodystrophy, and pancreatitis) which was significantly less as compared to 100.0% and 18.5% cases who developed ADR while on Stavudine and Efavirenz drugs, respectively.

Stavudine was significantly associated ($p<0.05$) with metabolic disorders like lipodystrophy, lactic acidosis, in our study and this finding was concordant with the finding of Nolan et al, that lipoatrophy is strongly and specifically associated with the use of certain NRTI drugs (stavudine more than zidovudine). Though Stavudine is increasingly associated with metabolic disorders, its lesser prevalence in our study may be due to the decreasing use of Stavudine in current regimens.

Our analysis revealed that, 78.9% (15 cases) and 10.5% (2 cases) who developed rash were on Nevirapine and Efavirenz drugs, respectively. The prevalence of rash/HSR was 6.3% in our study. In a Thai study, patients had a high incidence of NNRTI-related rash when treated with NVP + EFV or NVP once daily alone. NVP if used twice daily had the same rash incidence as EFV for rash of all grades. Females, and persons with earlier HIV disease or with a large rise in CD4+ cell count after starting therapy are at greater risk for NNRTI-related rash [16].

Nevirapine therapy can safely be replaced with efavirenz therapy for those who experience adverse reactions, because there is little evidence of rash cross-toxicity between the 2 drugs [17].

In our study, 15.3% of female cases had Anemia which was significantly more as compared to 6.3% of male cases and 6.9% of female cases had metabolic disorders which was significantly more as compared to 1.3% of male cases ($p<0.05$).

Agarwal *et al*., [9], found female patients to be more prone to develop zidovudine induced anemia. Metabolic disorders like lactic acidosis and lipodystrophy are known to be more common in women.

Thus, female gender was associated with a greater risk of developing anemia and metabolic disorders in our study population [18]. Though female gender is associated with development of rash in other studies, we did not find a significant association between the two.

Similarly we found that, 20.3% cases with CD4 count 100-250 had Anemia which was significantly more ($p<0.05$) as compared to 6.8% and 10.6% cases with CD4 count 251-500 and >500. This is in concordance with previous studies stating the correlation between low CD4 counts and development of anemia.

13.6% cases with CD4 count 100-250 had Nephrotoxicity which was significantly more ($p<0.05$) as compared to 1.5% and 1.0% cases with CD4 count 251-500 and >500 [19].

Multivariate analysis of post marketing clinical data showed that advanced age, low body weight, higher serum creatinine levels before starting tenofovir treatment, comorbidities (diabetes, hypertension, HCV coinfection) concomitant nephrotoxic medications, advanced HIV infection (low CD4 counts, AIDS) were risk factors for tenofovir induced GFR reduction.

Thus we conclude that low CD4 counts is a risk factor for the development of nephrotoxicity in patients who receive Tenofovir based ART [20, 21].

In our study, 9 (out of 19) patients who developed rash/HSR had a CD4 count of 251-500. In other studies, the development of rash and hepatotoxicity is associated with higher CD4 counts, however the findings in our study did not reach the level of significance.

13.6% cases with CD4 count 100-250 had neuropsychiatric disturbances compared to 6.8% and 2.9% with CD4 count of 251-500 and >500, respectively. The findings were not statistically significant. Though, this may suggest that lower CD4 counts predispose the HIV positive patient to the development of neuropsychiatric disturbances.

There was one mortality in the course of our study secondary to tenofovir induced acute renal failure. The lower mortality rate in our study population was probably due to the fact that majority of patients recruited in our study were patients attending the outpatient department of our hospital.

CONCLUSIONS

This study showed high incidence and prevalence of occurrence of ADRs in patients on HAART. Low CD4 count, Female Gender, Associated comorbidities were found to be risk factors for development of ADR. Anemia being the most common ADR due to high usage of Zidovudin can be prevented with serial monitoring with Hemoglobin levels and appropriate supplementation of vitamins and iron. Need of intensive monitoring for ADRs in ARTs thus seems to be a mandate. Patients education on ART-associated ADRs should be an important element of an effective HIV care package so as to facilitate reporting and subsequent management. Introduction of newer generation drugs with lesser toxicity profile in resource-limited settings is a prime mandate so as to ensure the provision of effective quality care to PLHIV.

LIMITATIONS

- Adverse drug reactions may have been underreported in our study owing to the higher rates of illiteracy of our study population.
- The association between viral load and adverse drug reactions could not be made due to our resource limited setting and financial constraints.
- Other risk factors like weight, BMI, concomitant drugs and comorbidities could have been studied as risk factors for adverse drug reactions.

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