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A RETROSPECTIVE STUDY OF ADVERSE DRUG REACTIONS TO HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY IN AN ANTIRETROVIRAL THERAPY CENTRE ATTACHED TO A GOVERNMENT MEDICAL COLLEGE AND HOSPITAL OF MAHARASHTRA.

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ABSTRACT

Background: Adverse drug reactions have been one of the most important limiting factors to the success of HAART. Hence, the present study was conducted to assess the incidence, causality and severity of ADRs to HAART, and to identify risk factors for ADRs in HIV-positive patients receiving ART in India.

Methods: It was a retrospective observational study of six months duration, conducted in a tertiary care hospital attached to SBH Government Medical College, Dhule. A total of 109 Patients reported with ADRs to HAART during July 2015-December 2015 were randomly included in the study.

Results: In the present study, Anaemia (76.52%), was the commonest ADR reported followed by skin rash (11.36%) and raised renal function test (6.06%). Out of 132 ADRs, 101 (76.52%) ADRs were belonging to haematological system. Zidovudine/Lamivudine/Nevirapine (ZLN) regimen (71.52%) use reported majority of ADRs. 120 (90.91%) ADRs were possible by Naranjo's causality assessment scale.

Conclusion: Anaemia was the commonly reported ADR from ART. , The findings of our study suggest that treating physicians must focus on early detection and prevention of ADRs in HIV infected patients of ART centers to improve the adherence to ART.

KEYWORDS : HIV/AIDS, Highly active antiretroviral therapy (HAART), ADRs

Introduction:

In India more than 2.39 million people are suffering with HIV/AIDS.[1] The first effective antiretroviral agent, Zidovudine was approved in 1987. The use of single drug (mono therapy) has been discontinued due to the high mutation rate of HIV[2] and three drug regimens are used as they are more effective [3] which is called as Highly Active Antiretroviral Therapy (HAART). Government of India has started free ART centers across the country through National AIDS Controlling Organization (NACO) on 1st April 2004. Today globally around 25 antiretroviral drugs are available to prolong the life of HIV/AIDS patients.[4]

The introduction of HAART has led to a significant reduction in AIDS related morbidity and mortality.[5] The widespread accessibility of antiretroviral therapy has transformed HIV into a chronic manageable disease with prolonged survival times. As with any chronic therapy, adverse drug reactions remain a major challenge in resource-limited settings due to a limited formulary and inadequately trained personnel. [6,7]

An ADR is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product (which in this case is HAART), which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.[8] ADRs have been one of the most important limiting factors to the success of HAART.[9] Unfortunately, up to 25% of all patients discontinue their initial HAART regimen because of treatment failure, toxic effects or noncompliance within the first 8 months of therapy.[5]The risk of adverse drug reactions (ADRs) arises because of the effect of the disease on the immune systems and the safety profiles of the complex ART drugs.[10]

ADRs in developing countries may differ from those in developed countries because of high prevalence of conditions such as malnutrition, tuberculosis and patients presenting with advanced HIV disease.[11] The major individual toxicities include bone marrow suppression (zidovudine [AZT]), pancreatitis (didanosine), hypersensitivity (abacavir), hepatic necrosis (nevirapine [NVP]), neuropsychiatric complaints (efavirenz), and nephrolithiasis (indinavir).[12] There is a lack of 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 is very important.

Hence, the present study was conducted to assess the incidence, causality and severity of ADRs to HAART, and to identify risk factors for ADRs in HIV-positive patients receiving ART in India.

Materials and Methods:

This retrospective study was conducted at National AIDS control organization (NACO) approved anti-retroviral therapy (ART) Centre attached to SBH Government Medical College, Dhule, Maharashtra. A total of 151 HIV/AIDS Patients (old and new cases) receiving highly active anti-retroviral therapy (HAART) during July 2015-December 2015 were randomly included in the study. Out of these, 109 patients had experienced more than one ADRs. Pediatric and Pregnant women patients receiving anti-retroviral therapy were excluded from the study. Patient's details such as name, age, sex, and 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.[13, 14] 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:

The results of the present study shows that Anaemia (76.52%) was the commonest ADR reported followed by skin rash (11.36%) and raised renal function test (6.06%). Nausea(1.51%), vomiting(1.51%), jaundice(0.76%), Hepatomegaly(0.76%), fever(0.76%) , fatigue(0.76%), neuropathy(0.76%) and Stevens johnsons syndrome(0.76%) were other ADRs reported. Patients receiving Zidovudine/Lamivudine/Nevirapine (ZLN) regimen (71.97%) reported higher number of ADRs followed by Stavudine/ Lamivudine/Nevirapine (SLN) (8.34%), Zidovudine/Lamivudine/ Effavirenz (ZLE) (6.82%), Tenofovir/Lamivudine/Nevirapine (TLN) (6.82%) and Tenofovir/ Lamivudine/ Effavirenz(TLE)(3.79%) regimen. Prevalence of anaemia was higher in patients receiving ZLN regimen (56.82%)(Table 1).

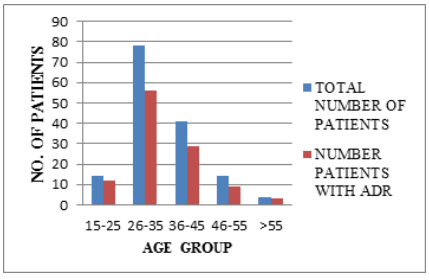
Table 1. Distribution and pattern of adverse drug reactions

(ADRs) depending on the HAART Regimen [n (%)]

Type of ADRs	ZLN	SLN	ZLE	TLN	TLE	SLE
Anaemia	75 (56.82%)	08 (6.06%)	07 (5.30%)	05 (3.79%)	04 (3.03%)	03 (2.27%)
Skin rash	09 (6.82%)	01 (0.76%)	01 (0.76%)	03 (2.27%)	01 (0.76%)	
Raised RFT	03 (2.27%)	01 (0.76%)	01 (0.76%)			
Nausea	02 (1.51%)					
Vomiting	02 (1.51%)					
Jaundice	01 (0.76%)					
Hepato-megaly	01 (0.76%)					
Fever	01 (0.76%)					
Fatigue	01 (0.76%)					
Neuro-pathy		01 (0.76%)				
SJS				01 (0.76%)		

Prevalence of ADRs was higher in 26-35 years of age group (51.38%) followed by 36-45 years of age group (26.61%)(fig.1).

Figure1: Age wise distribution of adverse drug reactions



Females (60.55%) had higher prevalence of ADRs as compared to males (39.45%)(Table 2).

Table 2. Showing gender wise distribution of total number of adverse drug reactions

Gender	Total patients (n)	Total number of patients developed ADRs(n)	Adverse drug reactions (%)
Male	43	52	39.4
Female	66	80	60.55
Total	**109**	**132**	**100**

Causality assessment showed that 90.91% ADRs belongs to possible category followed by probable (9.09%) (Table 3).

Table 3. Causality assessment of ADRs by Naranjo's causality assessment scale

Category	Number of ADRs	Percentage
Possible	120	90.91
Probable	12	9.09

Discussion:

In the present study, Out of 132 ADRs reported, commonest ADR was anaemia (76.52%) followed by skin rash (11.36%). Study by Bhuvana KB et al also found similar results, anaemia (55.06%) and rash (25.3%) were found to be most common type of ADRs.[15] But in previous studies by Nagpal M et al and Kiran reddy AV et al , where commonly reported ADRs belong to gastrointestinal and musculoskeletal system.[16,17] This variant in our study could be due to lack of awareness or under-reporting of ADRs. Therefore we recommend conducting seminars to educate treating physicians, health care professionals in ART center and patients about ADRs and pharmacovigilance program to reduce morbidity and mortality due to HAART therapy.

71.97% of ADRs were reported in patients receiving Zidovudine/ Lamivudine/Nevirapine (ZLN) regimen followed by Stavudine/ Lamivudine/Nevirapine regimen(8.34%).Study by Agu KA et al also found similar results ,of all patients who reported ADRs 39.9% were on Zidovudine/Lamivudine/Nevirapine regimen while 34.3% were on Stavudine/ Lamivudine/Nevirapine regimen.[18]

In our study, Anaemia (62.12%) was the most commonly reported ADR in patients who were on Zidovudine based regimen. Bhuvana KB et al also shows similar results, anaemia (55.06%) was seen with ZLN regimen, an improvement in the Hb level was observed on discontinuation of the Zidovudine based regimen.[15]

In the present study, the prevalence of ADRs was higher in 26-35 years of age group (51.38%) followed by 36-45 years of age group (26.61%).The results are in concordance with previous study results by Kiran Reddy AV et al. in which most of the patients were belonged to the age group of 21-40 years. [17] Hence we might have noticed majority of ADRs from middle age group as they are economically productive and sexually more active age group.

In the present study, Females (60.55%) had higher prevalence of ADRs as compared to males (39.45%). A study by Patel NM et al showed similar result, females had higher incidence of ADRs (1.80 ADR per patient, 117/65) than males (1.57 ADR per patient, 157/100).[19]

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%).[15]

Conclusion:

Adverse drug reactions to HAART in HIV patients are common and show wide variations. Studies on ADR pattern to HAART and reporting of ADRs in ART centers appear to be inadequate in our country. Thus this study provides a baseline data regarding the demographic characteristics of HIV/AIDS patients who had ADRs , risk factors , ART regimens causing ADRs and ADR profile to various HAART regimens.

Anaemia was the most commonly reported ADR from ART and those patients who received regimen containing zidovudine and nevirapine were more likely to suffer ADRs.

Thus, the findings of our study suggest that treating physicians must focus on early detection and prevention of ADRs in HIV infected patients of ART centers. Patient education on ART associated ADRs should be an integral part of HIV care so as to facilitate reporting and management.

The present study has some limitations. The study was conducted in only one nodal ART centre attached to a remote government medical college of Maharashtra ,India. These may exclude the actual number of HIV infected patients who were on ART and experienced ADRs. The period of study was not sufficient to assess long term ADRs as HIV/AIDS patients living longer with HAART. 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. Finally, further prospective study is recommended to overcome the limitations of retrospective study.

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