Monitoring Of Adverse Drug Reaction In Patients Receiving Antiretroviral Drug Treatment In A Tertiary Care Hospital

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Abstract: Background: Adverse drug reactions (ADRs) are frequently encountered among patients taking antiretroviral treatment (ART).The aim of this study was to describe the type and frequency of ADRs in patients receiving antiretroviral drugs. Material and Methods: 658 patients started on ART during the study period of 1 year were monitored for ADRs. The incidence and natures of ADRs occurring with different ART regimens were recorded. The study also assessed the severity, causality as well as the impact of ADRs on the patients' compliance. Results: Of 658 patients receiving ART, 33.7% patients (N=222) experienced ADRs. Among patients who developed ADRs there were more females 116(53%) than males 106(47%). Overall, 132(59.4%) of ADRs were reported by patients on ZLN regime with 54(24.3%) of these occurring in patients on SLN regime. The incidence of Anaemia in the patients who developed ADR is 25.2%, of Gastritis is 16.7%, of Cutaneous reactions is 14.9%, of Peripheral neuropathy is 11.3%, of CNS side effects is 11.3%, of Lipodystrophy is 10.8%, of Hepatoxicity is 5%, of Nausea, Vomiting in the patients is 3.60% and of Lipoatrophy is 1.4%. Among ADRs 59% of the reactions belong to grade II severity, 21.6% suffered from grade I, 18 % suffered from grade III, 1.4% suffered from grade IV severity.61.7% patients who developed ADRs required to substitute ART regime. Causality assessment revealed 69% ADRs were probable score 38% was of possible score. Conclusion: ADR is the single most common reason for poor adherence to treatment. Identifying risk factors for the occurrence of ADRs is of crucial importance to optimize the initial choice of ARVs regimen before initiating therapy and to adapt the pace of surveillance. With the increasing access to ART in India, it is prudent that ARV drugs are used judicially with regular monitoring of ADRs. [Zaparde S Natl J Integr Res Med, 2020; 11(5):56-60]

Key Words: Antiretroviral therapy, adverse drug reaction, human immunodeficiency virus, pharmacovigilance

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Introduction: Of an estimated 34 million people living with HIV/AIDS in 2010 globally, India has the third largest number of them. As per the 2008-09 HIV estimates, there are about 23.9 lakh people currently living with HIV/AIDS in India with an adult prevalence of 0.31 percent in 2009[1] With the availability of new antiretroviral drugs, there has been a decline in morbidity and mortality due to acquired immunodeficiency syndrome (AIDS).

Access to antiretroviral therapy (ART) has improved tremendously over the last few years due to implementation and enforcement of various strategies by National AIDS Control Organization (NACO). NACO has established ART centers in selected government hospitals which offer free treatment for HIV/AIDS and related opportunistic infections[2]. By December 2008, 197 ART centers were functioning in 31 states and union territories and more than 193 000 patients were accessing free ART through these centers[3]. By 2012, National AIDS Control Program III

(2007-2012) aimed to increase number of ART centers up to 250 where 3, 00,000 adults will be given free ART[2]. One of these centers is in B.J.Govt Medical College and Sassoon General hospital, Pune, where the present study was conducted. Highly active antiretroviral therapy (HAART) is the corner stone of management of patients with HIV/AIDS infection[4]. Consistent use is vital for drugs to be effective and to prevent emergence of resistance. However, ARV drugs are highly toxic and are associated with various adverse drug reactions (ADRs) due to which many patients require withdrawal of the drug or even discontinue the treatment resulting in treatment failure[5].

Hence, monitoring and reporting of ADRs in HIV/AIDS patients receiving ART assumes great importance. There is paucity of data on ADRs to ART in Indian population. Keeping this in view, the present study was designed to identify the ADRs in patients receiving ART and to assess their impact on the compliance to the prescribed treatment.

Material and Methods: It was a prospective, observational study of adverse effects of antiretroviral drugs in patients of HIV, in whom the drug treatment was initiated. The study was carried out in ART center at B.J.Govt Medical

College and Sassoon General Hospital. Approval from Institutional Ethics committee was obtained and written consent from patients was taken before conducting the study.

The study was conducted from January 2012 to February 2013 in patients of either gender. 658 patients started on ART during the study period were monitored for ADRs. Patients were also given the information about the study in the language which they understand.

Before starting HAART therapy the following tests were done: Hemoglobin, Total leucocytes count, differential leukocyte count and CD4 count. Other tests were carried out as per clinical condition. Five types of HARRT regimes were used:

1. Zidovudine Lamivudine Nevirapine (ZLN)
2. Stavudine Lamivudine Efavirenz (SLE)
3. Stavudine Lamivudine Nevirapine (SLN)
4. Zidovudine Lamivudine Efavirenz (ZLE)
5. Efavirenz monotherapy

Drugs Were Used In A Dose As Specified Below: Zidovudine 300mg twice daily, Lamivudine 150 mg twice daily, Efavirenz 600 mg once daily, Stavudine 30 mg twice daily, Nevirapine 200 mg once daily for 14 days, followed by 200mg twice daily.

Allotment of HAART regimes was based on physician's judgment. Enrolled patients were monitored for adverse effects of antiretroviral drug regime on 15th day ,1st, 2nd, 3rd, 4th, 5th and 6th month consecutively as and when needed and ADRs reported. In addition the patients coming in between the scheduled follow up period for their complaints were also monitored for adverse reactions to ART.

These adverse effects were recorded from the patients directly on case record form, and on CDSCO ADR reporting form and causality assessment was done using Naranjo scale. The patients with severe ADR were referred to appropriate clinical departments by the treating physician at ART centre and were followed up.

Result: This is a prospective study of adverse effects of ART in HIV patients, enrolled from January 2012 to February 2013. It includes all patients attending scheduled follow-up interview. Those who reported adverse reaction patients in between were followed up according to NACO guidelines. Among 658 patients who were started on ART during the period of 14 months 222 patients developed adverse drug reactions of various severity grades were recorded and followed up till recovery. Data was analyzed of patients who developed ADRs

Age Group And Gender Wise Distribution Of Patients: 73% (N=162) of the patients who suffered ADR were in the age group of 20-40 years of age 27% (N=60) of the patients were above 40 years age. There were 47.75% (106) men and 52.25% (116) women in the study.

Stage of AIDS and Mode of transmission: WHO clinical stage categorization of the patients, 63%(N=162) of the patients belonging to stage I and II, 18.5%(N=60) each belonging to stage III and IV heterosexual route of transmission is the most common route of transmission with contributing 96% of cases.

CD4 Count And WHO Clinical Stage Of Patients Developing Adrs: The mean CD4 count for Patients with WHO clinical stage I is 178±62.5 SD and median Value of 168.The mean CD4 count for patients with WHO clinical stage II is 202.8±131.5 SD and median value of 171. The mean CD4 count for patients with WHO clinical stage III is 212±129 SD and median value of 184.The mean CD4 count for patients with WHO clinical Stage IV is 174±52 SD and median value of 168.

Drugs Regime in Patients: Zidovudine + Lamivudine + Nevirapine (ZLN) regime contributes to 60% (N=132) And Stavudine + Lamivudine + Nevirapine (SLN) to 24% (N=54) of the total prescriptions. This is followed by Zidovudine + Lamivudine +Efavirenz (ZLE) 9% (N=20), Stavudine + Lamivudine + Efavirenz (SLE) 5% (N=11), Efavirenz monotherapy 2% (N=5)

Height And Weight Of Patients: The mean height of all 116 female patients is 155 cms ± 8.66 cms SD and mean height of all 106 male patients is 170 cms ± 8.80 cms SD. The median height of all 222 is 161.5cm. The mean weight of female patients is 46 kg ± 6.40 kg SD and means weight of male patients is 49 kg ± 6.33 kg SD. the median weight of all patients is 47.5Kg.

Table 1: ADRs And Prescribed Drug Regimen, Incidence Of ADRs:

Regime / ADRs	ZLN	SLN	ZLE	SLE	Efavirenz
Anaemia	55	00	01	00	00
CNS S/E	00	00	17	08	00
Cutaneous Reactions	29	04	00	00	00
Gastritis	36	00	01	00	00
Hepatotoxicity	04	00	01	01	05
Lipoatrophy	00	03	00	00	00
Lipodystrophy	00	23	00	01	00
Nausea,Vomiting	08	00	00	00	00
Peripheral Neuropathy	00	24	00	01	00
Total	132	54	20	11	05

The distribution of ADR to prescribed drug regime 59% adverse effects occurred to ZLN regime, 24% to SLN regime, 9% to ZLE regime,6% adverse effects occurring to SLE regime and 2%occurring to Efavirenz monotherapy. The incidence of occurrence of anaemia in the patients who developed ADR is 25.2% and of Gastritis is 16.7% and of cutaneous reactions is 14.9% and of peripheral neuropathy is 11.3% and of CNS side effects is 11.3% and of lipodystrophy is 10.8% and of hepatoxicity is 5% and of Nausea, Vomiting in the patients is 3.60% and of lipoatrophy is 1.4%.

Table 2: Adrs And Severity Grade:

Symptoms	Gr1	Gr2	Gr3	Gr4
Anaemia	08	11	14	00
Cns S/E	11	10	04	00
Cutaneous Reactions	05	18	08	02
Gastritis	10	23	04	00
Hepatotoxicity	02	09	00	00
Lipoatrophy	01	02	00	00
Lipodystrophy	06	14	03	01
Nausea,Vomiting	02	05	01	00
Peripheral Neuropathy	03	16	05	01

59% of the reactions belong to grade II severity, 21.6% suffered from grade I, 18 % suffered from grade III, 1.4% suffered from grade IV severity.

Causality assessment and ADRs with 69% of patients having probable as causality assessment on Naranjo scale.

Table 3: Adrs And Causality Assessment:

Symptoms	Probable	Possible
Anemia	39	17
CNS S/E	15	10
Cutaneous Reactions	24	09
Gastritis	24	13
Hepatoxiity	10	01
Lipoatrophy	03	00
Lipodystrophy	16	08
Nausea Vomiting	06	02
Peripheral Neuropathy	16	09

Table 4: ADRs And Treatment Intervention:

Symptoms	Changed Regimen	Symtomatic Treatment	Treatment Continued	Treatment Stop
Anemia	33	02	00	21
CNS S/E Vivid dreams,Drowsiness	16	02	01	06
Cutaneous Reactions	18	02	01	12
Gastritis	20	00	01	16
Hepatotoxicity	06	01	00	04
Lipoatrophy	01	00	00	02
Lipodystrophy	18	00	01	05
Nausea,Vomiting	05	00	00	03
Peripheral Neuropathy	20	00	00	05

ADR and treatment intervention comparison with 37.5% patients who developed anaemia ADR and treatment intervention comparison with 37.5% patients who developed anaemia patients have

stopped the treatment 58% of patients have changed ART regime and 54% of patients who have cutaneous reactions also changed ART regime.

Discussion: This is a prospective study on the incidence of ADRs in HIV-positive patients receiving HAART. The study observed significant ADRs associated with the use of HAART in the ART Centre. In this study total 222 patients the age group 18-59 years, 106 men and 116 women (were put on various regimes according to NACO guidelines).

Mean weight of the female patients was 46±6.40 SD kg and that of male patients was 49±6.33 SD kg. In a similar study C.George et al [7] in Kerala reported mean body weight of 47.45kg and 50.89 kg of females and males respectively at baseline.
Kelsey K Case et al. in his study of understanding the modes of transmission model of new HIV infection and its use in prevention planning shows heterosexual route of transmission as the most common route of transmission of HIV in third world countries account for nearly 90% of transmission of HIV

Mean CD4 count in the patients experiencing ADRs was 194cells/mm3 with median CD4 count of 172. This is in agreement with findings of González-Martín G et al who studied adverse drug reactions (ADRs) in patients with HIV infection and correlated it with their CD4 counts[8]. In this study among the patients who had ADRs the incidence of anaemia was 25.2%, of nausea, vomiting and gastritis 19.6%, and cutaneous reaction was 14.9%. These were commonly reported ADRs. RR Modayii et al reported anaemia and vomiting as most common ADRs to ART[9].

Peripheral neuropathy was observed in 44% patients who were on Stavudine-containing regimen for more than 3 months. Of these 24 patients Stavudine was discontinued and all the patients recovered. In a study conducted by B Srikanth et al[10], peripheral neuropathy was found to be associated with Stavudine containing regime. In our study 1.8% of patients developed hepatitis on NVP containing regimens. The incidence of drug-related hepatitis in US and European trials has ranged from 1% to 10%[11]. Among patients who were receiving SLN regime, 54% patients developed Lipodystrophy and atrophy. In a study conducted by B Srikanth et al lipodystrophy and lipoatrophy were found to be associated with stavudine containing regime[12].

Limitations of the present study include small sample size and a short duration of study. The difference in sample size in the treatment regimens was so wide that appropriate statistics to compare the difference was not possible. Moreover, because of small sample size, ADRs which are uncommon and rare couldn't be identified.

Conclusion: Antiretroviral drugs are highly toxic and associated with myriad adverse drug reactions and that too with a very high frequency. These ADRs are adding to the problem of non-compliance which in itself is a very big issue with ART. Hence, it is prudent to recognize these ADRs as early as possible in the course of treatment. This goal can be achieved by regular monitoring and reporting of ADRs which is indispensable for improving the treatment outcome.

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