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A STUDY ON ADVERSE DRUG REACTIONS IN PATIENTS ON ANTIRETROVIRAL THERAPY IN A TERTIARY CARE HOSPITAL AT JAIPUR, RAJASTHAN

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Abstract
Background: The present study was conducted to know the status of ADRs caused due to the first line ART in the ART center of SMS Hospital Jaipur, Rajasthan. This study would be beneficial to the HIV infected patients, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment by promoting the early recognition of potentially serious adverse effects.
Methods: Hospital based Prospective, Observational study conducted after approval by research review board and ethics committee SMS Medical College Jaipur (Rajasthan). WHO definition of ADR was used (any response to a medicine which is noxious and unintended and which occurs at doses normally used in man). The detail of ADRs collected including suspected drug involved, treatment given for ADRs and outcome.
Results: Majority of ADRs were related to central and peripheral nervous system related 55 (47%) followed by gastro intestinal 28 (23.9%), dermatological 15 (12.8%), musculoskeletal 9 (7.7%) and metabolic 5 (4.3%).
Conclusion: Majority of ADRs were related to central and peripheral nervous system related followed by gastro intestinal.
Keywords: ADRs, HIV, WHO.

Introduction

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes Acquired Immunodeficiency Syndrome (AIDS), a condition in which progressive failure of the immune system allows life threatening opportunistic infections and cancers to thrive.[1]

In India, the National AIDS Control Organization (NACO) publishes guidelines regularly, outlining the steps for diagnosis and treatment of HIV infection, the most recent ones being those published in October 2018 recommended the use of tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV) as a fixed-dose combination in initiating ART in all future treatment-naïve patients.[2]

According to these guidelines ART is now being initiated regardless of the WHO stage and CD4 counts, the ideal time to start ART is before the patient presents with an opportunistic infection based on the patients' informed decision to start. More often than not, once started the therapy has to be continued for life.

The goals of antiretroviral therapy (ART) in HIV infections comprises of prolongation of life and improvement in quality of life with greatest possible reduction in viral load for as long as possible.

However, attempts to achieve these goals with standard antiretroviral pharmacotherapy are fraught with a diverse range of unwelcome adverse drug reactions (ADRs). Many of these drugs are known to cause adverse effects, which can range from being mild to even life threatening [3]

In the event of drug toxicity and severe adverse drug reactions, the offending drug(s) must be discontinued and changed to other drugs from within respective ARV options.

Studies comparing different standard regimens showed moderate-quality evidence indicating that a once-daily combination of tenofovir, lamivudine and efavirenz is less frequently associated with severe adverse events and has a better virological and treatment response compared with other once- or twice-daily regimens [4,5] However, they are not entirely devoid of adverse reactions.

ADR surveillance is an integral component of monitoring and evaluation in the national AIDS control Programme. The goal of monitoring is to detect the early toxicities and adverse effects in order to support the safe use of ART, thus improving the quality of care and treatment outcomes and to inform national guidelines and global policies on the use of first line ART in adults. However, attributing a single drug to a particular adverse event is cumbersome, as HAART comes as a three or more drugs regimen.

The present study was conducted to know the status of ADRs caused due to the first line ART in the ART center of SMS Hospital Jaipur, Rajasthan.

This study would be beneficial to the HIV infected patients, with the ultimate goal of improving the tolerability and effectiveness of HIV treatment by promoting the early recognition of potentially serious adverse effects.

Materials and Method

Study design: Hospital based Prospective, Observational study after approval by reaserch review board and ethics committee SMS Medical College Jaipur (Rajasthan)

Study place: Medicine OPD, Medicine Wards, ART Centre of SMS Hospital, Jaipur

Study duration: October 2018 to July 2019

Sample size: Sample size was calculated to be 86 cases as per previous study having incidence of adverse drug reactions 90.6% with relative error 7%, alpha error 0.05% and power 80% in round off about 20% attrition. To increase the efficacy total 110 cases were enrolled for the study. All 110 patients completed the study. There were no drop out in our study.

Inclusion Criteria

All Newly Diagnosed HIV/AIDS patients taking first line Anti Retroviral therapy.
Patient age more than 18 years.

Exclusion Criteria

Patients with Pre existing:

Liver disease
Renal dysfunction
Gastrointestinal Disease
Cardiac Diseases
Major Neuropsychiatric illness
Malignancy.
Pregnancy.
Patients those not giving consent

Methodology

Data regarding patient demographics and clinical information were collected in a prestructured pro forma. Basic investigation like CBC, blood sugar, renal function test, liver function test, lipid profile, hepatitis marker, VDRL, urine routine microscopy, chest x ray and CD4 count was done at the baseline. Details regarding HIV infection were also collected with respect to mode of infection, duration of illness, clinical signs and symptoms, WHO staging of the disease, presence of opportunistic infections and concomitant treatment with ATT. Patients were followed for next six month on monthly basis and data collected by interviewing patients regarding development of any ADRs. Suitable investigation was performed as per clinical indication.

ADR Monitoring: WHO definition of ADR was used (any response to a medicine which is noxious and unintended and which occurs at doses normally used in man). The detail of ADRs collected including suspected drug involved, treatment given for ADRs and outcome.

Statistical analysis:

Qualtitative data is presented as percentage of proportion. Quantitative data is present as mean and standard deviation. Significance of difference in proportion was inferred by Chi- square test. Significance of difference in mean was inferred by Unpaired t-test

The level of significance was kept at 95% for all statistic analysis. P value of less than 0.05 was taken as significant.

Results:

Table 1: Sociio-demographic profile

Age in years	Number of cases	Percentage
18 – 30	32	29.10%
31 – 40	47	42.70%
41 – 50	22	20.00%
51 – 60	7	6.40%
>60	2	1.80%
Sex (M:F)	66:44	

Majority of the patients enrolled in the study group were between 31 – 40 years age group (42.1%) followed by 18 – 30 years age (29.1%) Two patients were more than 60 years of age. In total 110 study patients 66 were male (60%), and 44 were female (40%).

Table 2: Number of adverse drug reaction in patients

Number of ADRs	Number of patients	%
0	58	52.73
1	14	12.73
2	22	20.00
3	6	5.45
>4	10	9.09
Total	110	100.00

In the total study of 110 patients 58 patient did not developed any ADRs. 14 patients developed one ADRs. 22 patients developed two ADRs,6 patients developed three ADRs and 10 patients developed more than four ADRs. Majority of the patients who developed $\geq$ 3 ADRs was taking drugs for concomitant oppertunistic infection.

Table 3: Distribution of ADRs with WHO staging of patients

WHO CLINICAL STAGE	Total patients	ADRs Present(one or more)	Percentage
1	83	39	46.99
2	17	8	47.06
3	9	5	55.56
4	1	0	0.00
Total	110	52	47.27

Chi-square = 1.147 with 3 degrees of freedom; P = 1.000

Patient in WHO stage 1 was maximum in number in study poulation. Maximum percentage of ADRs Were found in WHO stage 3 patients while minimum percentage of ADRs was found in patients with WHO stage 1

Table 4: Distribution of adverse drug reactions as per organ system affected

Adverse drug reactions	N	%
Gastrointestinal disorders	28	23.93
Central and peripheral nervous system disorders	55	47.01
Dermatological disorders	15	12.82
Metabolic disorders	05	4.27
Musculo Skeletal disorders	9	7.69
Hemotological disorder	01	0.85
Renal disorders	01	0.85
Miscellaneous	03	2.56
Total	**117**	100.00

Majority of ADRs were related to central and peripheral nervous system related 55 (47%) followed by gastro intestinal 28 (23.9%), dermatological 15 (12.8%), musculoskeletal 9 (7.7%) and metabolic 5 (4.3%).

Discussion

The present study included a total of 110 PLHIV who were put on first line ART regimen comprising of tenofovir, lamivudine and efavirenz (TLE). Majority of the study population were males (60%) with patients belonging to 31 to 40 years of age group representing the maximum (42.7%) study population. Out of total patients on this regimen, 52 patients (47.3%) experienced adverse drug reactions. 14 patients experienced one ADR (12.7%), 22 patients with two ADRs (20%), 6 patients with three ADRs (5.45%) and 10 patients with four or more ADRs(9%). Previous study done by Nikhil era et al[6] in 2017 on Monitoring adverse drug reactions in patients on TDF+3TC+EFV observed 69% ADRs, out of total 242 patients study 167 patients developed 451 ADRs in which 83 patients encountered with one ADRs, 57 patients with two ADRs and 27 patients with Three or more ADRS. In another study by S.Mukherjee et al [7] in 2017 observed 32.45% ADRs from various ART regimens including 16% ADRs developed on TLE regimen.

Sex of the patients did not have any side effect on development of ADRs. A study done by KB Bhuvana et al[8] in 2014 also not observed any significant difference in ADR between male (50.6%) and female (49.4%) in their study.

Our study revealed that nervous system related complaints accounted for the maximum number of reported ADRs (47%), followed by GI disorder (23.9%), dermatological disorders (12.8%), and musculoskeletal disorders (7.6%). Study done by Nikhil Era et al[6] on monitoring adverse drug reactions in patients on TDF+3TC+EFV also observed that maximum ADRs were related to neuro psychiatric disorders (43.24%), gastrointestinal disorders (21.95%)and dermatological complications (9.97%). Aboubacar Alassane Oumar et al[9] in their study "Adverse Drug Reactions to Antiretroviral Therapy (ART): Prospective Study in HIV Infected Adults in Sikasso (Mali)" in 2017 also observed neurological ADRs in 40.4%, gastro intestinal in 35.8%, cutaneous in 18.3% and hematological disorder in 5.5% patients on various ART regimens in their study with a total of 61.2% ADRs in the 178 patients enrolled.

Among the nervous system related ADRs insomnia (6.8%), headache (8.5%), numbness (5.9%), dizziness (13.6%) and depression (5.1%) were the commonest. For most patients, these side-effects resolved within 6–10 weeks of starting therapy, but for some patients, symptoms reappeared to wax and wane for long duration. Some studies have reported treatment discontinuation rates ranging from 4% to 46% related to neuropsychiatric side effectsof EFV.[10,11] Our study accounted for 47% nervous system related ADRs compared to previous study done by Nikhil Era etal[12] in august 2017, who observed 43.24% incidence of neuro psychiatric disorders on the same ART regimen. In our study no patient had to stop or changed the regimen due to these symptoms, reason may be due to better counselling of the patients about the expected side effects of the drug.

Various gastrointestinal disorders including anorexia, nausea, vomiting, abdominal pain /cramps, diarrhoea, dyspepsia were the most frequently observed ADRs in several studies. These types of ADRs appeared mainly during the first 12 weeks of therapy and were mild (grade

≤2) and transient in most patients. Our study revealed 23.9% gastro intestinal ADRs in which anorexia (14.5%) and abdominal cramps (6.84%) were the most frequent, followed by vomiting (1.7%) and diarrhoea. A previous study done by M.Nagpal et al [13]observed 42.4% gastro intestinal ADRs on various ART regimen and a study by AV Kiran reddy et al [14] on ADRs in HIV infected patients at Guwahati, in 2013 observed 31% GI related ADRs on various ART regimen. These are comparable to our results.

In our study dermatological ADRs accounted for 12.82 % of the total ADRs which included skin rashes, itching, pigmentation of nails and skin. Most of skin rashes were of mild grade. One of our patient had severe intolerant skin rashes for which efavirenz was replaced with nevirapine and she tolerated it well. A previous study done by S. Mukherjee et al[7] in 2016 observed 7.8% dermatological disorder on various ART regimens and Kashifullah et at[15] observed 18.8% dermatological ADRs in 2016 at Malaysia . In our study the morbilliform eruption, often referred to as a maculopapular rash was the most common type of reaction after treatment.

In the present study musculoskeletal complications accounted for 7.7% of the total ADRs. Generalized weakness, bodyache and muscle cramps/pain were common amongst various musculoskeletal complaints. A previous study done by Nikhil era et al[6] showed 10.2% of musculoskeletal complications on the same regimen.

Conclusion

Majority of ADRs were related to central and peripheral nervous system related followed by gastro intestinal.

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