A Prospective Study of Adverse Drug Reactions During First Six Months of Therapy due to HAART in HIV Infected Patients at a Tertiary Care Hospital in Indore, India

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ABSTRACT

Introduction: Acquired Immunodeficiency Syndrome (AIDS) is a global problem; global statistics till March 2015 revealed that 36.9 million people were living with HIV; where 15 million people accessing antiretroviral therapy. From an antiretroviral perspective, HAART is a potent form of therapy but it often fails owing to non adherence. One way of increasing the adherence is by focusing on prevention of adverse effects wherever possible.

Material and method: This is prospective, observational study conducted at a single ART centre of tertiary care hospital. The adverse drug reactions occurring during first six months following initiation of antiretroviral regimens were observed.

Results: A total of 292 patients were recruited, out of which 132 had shown adverse drug reactions (ADR) to antiretroviral regimen. Out of these, gastrointestinal ADRs were the most common (41%) perceived reactions. A total 64 patients on Zidovudine developed anemia (10%), of which 26 patients required change in regimen. Sixteen patients received Nevirapine developed skin rash (5%) and two patient (0.6%) developed Steven Johnsons syndrome.

Conclusion: Most of the antiretroviral associated ADRs were mild, suggesting a good tolerance to antiretroviral medicines. So, a proper counseling and proper observation during this initial phase could probably increase the adherence of patients with antiretroviral medication.

Keywords: HIV, HAART, adverse drug reaction, anemia, skin rash, nevirapine

INTRODUCTION

Acquired Immunodeficiency Syndrome (AIDS) is a global problem; global statistics till March 2015 revealed that 36.9 million people were living with HIV; where 15 million people accessing antiretroviral therapy. There were 2 million newly HIV infected cases and 1.2 million deaths due to AIDS-related illnesses.[1] Introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS related mortality.[2,3,4] At present drugs belonging to classes of nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, fusion inhibitors, entry inhibitors-CCR5 co-receptor antagonist and HIV integrase inhibitors are approved by Food and Drug Administration for treatment of HIV infection.[5] Adverse effects due to antiretroviral can be class specific or can be individual drug specific.[6] Very few prospective studies regarding antiretroviral associated adverse effects are available in Indian Literature,[2,7,8,9,10] but such data might not be up-to date or the data is not relevant to other medical set-up.

From an antiretroviral perspective, HAART is a potent form of therapy but it often fails owing to non adherence. One way of increasing the adherence is by focusing on prevention of adverse effects wherever possible. Clinician should be able to distinguish serious/life threatening adverse effect from those that are self limited/mild.[7] Of all the patient initiated on HAART, up-to 25% discontinue their therapy because of treatment failure, toxic effect or non-compliance within first 8 months of herapy.[11] Hence, it is very important to monitor and report adverse drug reaction associated with antiretroviral therapy. This study was performed to assess the incidence and pattern of adverse drug reaction associated with antiretroviral therapy in our set-up.

MATERIAL AND METHOD

This is prospective, observational study conducted at ART centre, Department of Medicine, MY Hospital, Indore (M.P). The primary end point was completion of six month follow up, all patients started on first line HAART regimen from June 2013 to March 2014 were screened for recruitment. The study protocol along with the proforma and informed consent was approved by Institutional Ethic Committee before starting. The study proforma contained patient identification data, personal history, family history, treatment history, lab-

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oratory investigations, ADR details & its assessment and patient follow up details.

Inclusion criteria

All adult HIV positive patients-

A) newly registered, started on first line art regimen.
B) started on first line art regimen, already registered.
C) having age of after18-year and Above.

Exclusion criteria

1. Seriously ill patient.
2. Cancer patients.
3. Children below the age of 18 years
4. Patient who were suffering from active renal disease, liver diseases and multi-system diseases like diabetes mellitus, hypertension, cardiovascular disease, cerebrovascular disease and psychiatry illness.

Essential laboratory investigations such as complete blood count, erythrocyte sedimentation rate, liver function test, renal function test, blood sugars, VDRL, HBsAg, CD4 count. Additional laboratory investigations like chest radiograph, thyroid screen were performed whenever needed.

STATISTICAL ANALYSIS

Descriptive statistical analysis has been used in the present study. However for statistical analysis of qualitative variables Chi square test were performed.

RESULT

A total of 423 patients were screened during study period, out of which 292 were recruited in the study. There were 206 males, 84 females and 2 transgender in the study.

Gender wise and age group wise distribution of HAART regimen has been described in Table 1 and Table 2, respectively. Most number of the patients received ZLN (43%) as a first line HAART and ZLE (24%), TLN (16%) and TLE (13%). One patient received SLN. According to the age, maximum number of the patients distributed between 18 to 49 years of age. 108 patients were between 30-39 years of age, of which 40 developed ADRs. A total of 66 and 78 patients between age group18-29 and 40-49 of which 34 and 36 patients respectively developed ADRs.

Distribution of adverse drug reaction according to the regimen has been given in Table 3.

Gastrointestinal ADRs were the most common perceived reactions, 102 patients developed this (41%) ADRs, of which nausea and vomiting were most common. A total 64 patients on Zidovudine developed anemia (10%), of which 26 patients required change in regimen. Sixteen patients received Nevirapine developed skin rash (5%) and two patient (0.6%) developed Steven Johnsons syndrome.

Distribution of ADRs according to CD4 counts have been

	Patents with ADRs	Patients with no ADRs	Percent of patient ADRs	Total
Female	42	42	50%	84
Male	90	116	44%	206
Transgender	0	2	0	2
Total	132	160		292
Sex * ADRs group Cross tabulation				

Table-1: Gender and ADRs distribution in patients on ART

Age group and ADRs group distribution					Percent
		ADRs Group		Total	
		Reported ADRs	No ADRs		
age group (years)	18-29	36	32	68	52
	30-39	42	68	108	39
	40-49	38	42	80	47
	50-50	12	10	22	54
	≥60	4	8	12	33
Total		132	160	292	

Table-2: Age group and ADRs distribution

ADRs	ZLN	ZLE	TLN	TLE	Others	
Abdominal pain	4	2	0	6	0	12
Anemia	22	8	2	0	0	32
Constipation	2	0	2	0	0	4
Deranged amylase	0	2	0	0	0	2
Deranged liver function	4	0	2	0	0	6
Diarrhea	2	4	2	4	0	12
Dizziness	2	0	4	0	0	6
Dyslipidemia	8	4	2	0	0	14
Fever	4	4	0	0	0	8
Gastritis	6	2	0	0	0	8
Generalized body ache/myalgia	2	0	0	0	0	2
Leg swelling	8	0	0	0	0	8
Nausea, vomiting	20	22	4	8	2	58
Skin rash	10	0	4	2	0	16
Steven Johnsons syndrome	2	0	0	0	0	2

Table-3: ADRs distribution with ART regimen

represented in table 4, we could not find any statistical significant relation of ADR with CD4 counts (Pearson Chi-square p=.33).

DISCUSSION

The likelihood of developing an adverse drug reaction was highest in the first six months of commencing antiretroviral therapy. Xavier et al.[12] proffered an explanation that early occurrence of ADRs is an expression of a Mechanism of intrinsic intolerance rather than of a time-dependent toxic accumulation process. Close monitoring of patients within this time frame is thus imperative to prevent the occurrence of severe ADRs, improve adherence as well as improve documentation of ADRs.

However 45% of the reported ADRs occurred within 12- 24 months of commencing ARTs. This calls for the need to intensify long term ADR monitoring in patients on ART. Some studies have proposed time-dependent toxic accumulation as the mechanism of developing an ADR long after commencing medication. Thus monitoring for ADR should be an ongoing process. Adding a laboratory component to the ADR screening would go a long way in determining biochemical markers that would help to improve patient management.

Since adverse drug reactions are 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 ARTs regimen before initiating therapy and to adapt the pace of surveillance to each unique situation.[12]

CD4 counts	Total number of patients	Patients developed ADRs	Percent
0-49	19	8	42
50-99	15	8	53
100-199	43	23	53
200-349	48	26	54
≥350	21	13	61

Table-4: CD4 counts and ADRs distribution

In our study greater proportion of women participants experienced ADRs, compared to men, similar to other studies conducted Bonfati et al.[13] Though the population of patients on Stavudine based regimen was small, compared to AZT and TDF, our data shows that patients on AZT were likely to report an ADR than those on TDF. A multisite trial in Africa, found tenofovir therapy to be associated with 1.3% risk of developing significant nephrotoxicity which was comparable to other regimen,[14] but in our study no significant nephrotoxicity was observed. A closer look at the drug profile and toxicity of TDF is urgently needed to better understand its tolerance in patients in this setting.

Gastrointestinal side effects were most commonly reported (52%), mild to moderate in severity and required no change in first line ART regimen. Incidence of anemia was low at 4% and occurred exclusively in patients on AZT. This is similar to other studies conducted in Nigeria, Coˆ Te d'Ivoire, Haiti and India that observed anemic rates of 3%-12%.[7-10,14]

Most of the reported ADRs (71%) were mild to moderate and self limiting in nature. This suggests good tolerance level to ARTs in general.

While other studies have associated low CD4 count at treatment initiation as a risk factor for ADR,[14] our study did not show any association between CD4 cell count and clinical stage with ADRs.

This study has some limitations. The study was shorter in duration and since this study provided information on short term adverse effects, we may have missed late onset ADRs in these patients. The small sample size of patients on Stavudine based regimen limits our ability to compare ADR reported by this group with other regimen groups.

Major adverse effect found in our study has been compared

Characteristics	Our study	Lihite et. al.[8]	Bhatnagar et.al.[9]	Divakar et.al.[2]	Bhuvana et.al.[10]	Sharma et.al.[7]
Follow-up duration (in months)	6	-	18	8	6	24
total subjects studied	292	300	129	400	158	90
Subjects with adverse reaction (%)	45	31	75	27	-	71
Male/Female with adverse reaction	90/42	70/23	-	64/36 (no of adverse events)	80/78	90/64
Gastro-intestinal adverse reaction	35% (102/292)	17% (50/300)	30%	6.2% (26/400)	10% (17/158)	20% (18/90)
Skin rash	5% (16/293)	13% (38/300)	24%	6.2% (26/400)	25% (40/158)	10% (9/90)
Steven Johnson Syndrome	0.6% (2/292)	0.6% (2/300)	-	1% (4/400)	-	3.3% (3/90)
Anemia	10% (32/292)	5.3% (16/300)	28%	6.5% (26/400)	55% (87/158)	20% (18/90)
Relation of adverse reaction to CD4 count	No relation found	-	More in CD4 count <200 cells/ mm^3	-	More in CD4 count <250 cells/mm^3	-

Table-5: Comparison of major adverse effect found in our study with other recently performed, prospective, Indian studies

with other recently performed, prospective, Indian studies in Table 5.

CONCLUSION

This study provides information about adverse events occurring during short, but crucial initial six months of initiation of HAART. We have found that age group of 18 to 49 years was maximally affected; also gastrointestinal adverse events were most common. Important to note that most of the HAART associated ADRs were mild, suggesting a good tolerance to antiretroviral medicines. So, a proper counseling and proper observation during this initial phase could probably increase the adherence of patients with antiretroviral medication.

ABBREVIATIONS

AIDS - Acquired Immunodeficiency Syndrome,
HAART - Highly active Antiretroviral Therapy,
ARD - Antiretroviral (drug),
AZT - Zidovudine (also known as ZDV),
CD4 - T-lymphocyte CD4+,
GI - Gastrointestinal,
HIV - Human Immunodeficiency Virus,
NVP - Nevirapine,
ZLE - Zidovudine + Lamivudine + efavirenz,
ZLN - Zidovudine + Lamivudine + Nevirapine,
TLN - Tenofovir + Lamivudine + Nevirapine,
TLE - Tenofovir + Lamivudine + Efavirenz,
SLN - Stavudine + Lamivudine + Nevirapine,
TDF - Tenofovir Disoproxil Fumarat

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