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Pharmacovigilance Study of Antiretroviral Drugs in Tertiary Care Hospital - A Prospective Study

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Abstract

Background: *Anti-retroviral therapy present today has reduced morbidity and prolong life span of patients. Globally physicians are faced everyday with problems of adverse drug reactions (ADRs). World health organization focus on studies reporting adverse reactions for safety of patients. Such studies leads to revision of ART guidelines.*

Aim: *To carry out Pharmacovigilance study of antiretroviral drugs in our tertiary care hospital.*

Objectives: *To detect, assess and classify ADRs in patients receiving Highly Active Antiretroviral Therapy (HAART).*

Material and Methods: *This was a prospective, observational study carried out at Government medical college and tertiary care hospital Latur, Maharashtra. Both old and newly diagnosed patients of either sex and all age group receiving HAART were included in this study. Data was collected in suspected adverse drug reaction reporting form by using patient's record and analysis was done.*

Results: *A total 157 patients presented with 223 ADRs during this study. Among them 106 were female and 51 were male. Females in the age group 20-40 years were most commonly affected. Common ADRs observed included anemia, dizziness, giddiness, skin rash. Most of ADRs were Type A, probable, non serious, moderate in severity, probably preventable.*

Conclusion: *This pharmacovigilance study of antiretroviral drugs concludes that the risk factors for development of ADRs were female gender, age group 20-40 years, people in rural area, labor by occupation taking ZLN and TLE regimens. So there is need of continuous monitoring of ADRs.*

Keywords: *Phamcovigilance, ADRs, Antiretroviral therapy, Suspected ADRs reporting form.*

Introduction

The word pharmacovigilance has derived from the Greek word pharmacon means "drug" and the Latin word vigilare means "to keep awake or alert or to keep watch".[1] By definition, pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems. It is fast emerging as an important approach for the early detection of unwanted effects of the drugs and to take appropriate regulatory action if necessary. This may ensure the safer use of drugs.

Current pharmacovigilance is predominantly based upon spontaneous reporting system (SRS). SRS depends on the practitioners to voluntarily identify, investigate and report the suspected adverse drug reactions (ADRs). They are asked to report all suspected drug related adverse events including those suspected to have been caused by herbal, traditional or alternative medicines; also those seemingly insignificant or common adverse reactions and all the suspected drug interactions and serious ADRs. The main disadvantage of this approach is the potential for selective reporting and underreporting. The main cause of underreporting is less awareness among the public and health professionals.[2]

The disease acquired immunodeficiency syndrome (AIDS) is caused by Human Immunodeficiency Virus (HIV) which mainly affect CD4 cell and decreases immunity of person which makes patient susceptible to various secondary infections. Globally more than 35 million people are affected by HIV. It becomes most serious health and developmental challenge. In India, National AIDS Control Organization (NACO) has established Anti-Retroviral Therapy (ART) centers in various government hospitals of India to provide free antiretroviral treatment to the people living with HIV.

Antiretroviral therapy (ART) is the only option for treatment of HIV as no effective vaccine is still available to prevent the infection. Highly active antiretroviral therapy (HAART) is now the standard therapy for treatment of HIV. Anti-retroviral therapy present today has reduced the morbidity associated with HIV infection to prolong the life span of patients.[3] Unfortunately, up to 25% of all patients discontinue their initial HAART regimen because of ADRs or noncompliance within the first 8 months of therapy.[4]

WHO focuses on studies reporting ADRs for safety of patients. These report leads to revision of ART guidelines. Reporting of such ADRs may provide information in clinical practice to identify new ADR and modify knowledge about known prevalence of ADRs. Obiako et al has concluded in their study that current antiretroviral regimens are associated with various forms of ADRs, thus there is need to strengthen pharmacovigilance and proper education of patients on the possible adverse reactions of ARV regimens.[5] A study conducted by Bhuvana et al concluded that identifying risk factors are of crucial importance to optimize the initial choice of ARVs regimen before initiating therapy and to prevent severity and complications caused by ART, thereby improving the quality of care to patients on ART.[6] So our 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 reporting of ADRs amongst the patients receiving HAART at our tertiary care hospital.

With this background this study was planned with following objectives:

1. To identify adverse drug reactions in patients receiving Highly Active Antiretroviral Therapy (HAART).
2. To assess and analyze the ADRs according to their demographic distribution, risk factors and presentation.
3. To do causality assessment of the ADRs.
4. To classify ADRs and to study outcome of these ADRs.

Material and Methods

This prospective, observational study was conducted in patients receiving antiretroviral therapy in outpatient department (OPD) and in patient department (IPD) of government medical college & hospital, Latur, Maharashtra.

The study was approved by the Institutional Ethics Committee. Written inform consent of patients was taken before enrolment of patients in the study. Patients had also given the information about study in the language they understood.

Patients satisfying following criteria were included in this study:

Inclusion Criteria

1) Both old and newly diagnosed patients receiving HAART with suspected ADRs that were confirmed as per WHO definition.
2) Patients of either sex and all age groups.
3) Indoor and outdoor patients with ADRs due to HAART confirmed by physicians.

Exclusion Criteria

1) Patients with suspected ADRs due to other concomitant drugs like anti- tuberculosis drugs, cotrimoxazole etc.
2) Patients not willing to participate in the study.
3) Noncompliance with the ART treatment.

Sources of Data

Data was collected by using Suspected ADRs reporting form provided by Indian Pharmacopoeia Commission, Ghaziabad under PVPI. All the clinical events including laboratory abnormalities suspected to be caused by antiretroviral drugs were taken as suspected ADRs.

Patients with suspected ADRs to HAART agents were studied under following parameters: details of patients &adverse drug reaction**,** lab investigations, suspected drug, all other concomitant drugs used, past and present medical history.

Some additional information like locality, educational status and occupation of patients with suspected ADRs to HAART agents was collected in documentation form prepared for the study. Other parameters of study like type of ADRs, preventability, severity, management and treatment of the ADRs was also noted in documentation form.

After confirmation ADRs to HAART agents by treating physicians, the information about ADRs was compiled and analysed to establish a causal link between the suspected drug and the adverse events. Causality assessment of these ADRs was done by Naranjo's scale.[7,8] Then information of all these ADRs were forwarded to national coordinating centre by using Vigiflow software (Version 5.3). Rawling and Thomsons criteria was used for classification ofADRs.[9,10]

Adverse drug reactions were also classified as serious and non serious depending upon events outcome. A serious adverse event or reaction is any untoward medical occurrence that at any dose results in death, requires hospitalization or prolongation of existing hospitalization, results in persistent disability and is life-threatening.[2,11]

Preventability of ADRs was assessed by using Modified Schumock and Thornton scale.[12] Modified Hartwig's and Seigel scale was used for assessment of severity.[12] The ADRs thus reported were assessed for demographic details, duration between administration of drug and occurrence of ADRs and organ system affected. System organ classification was done by using various terminology given in WHO adverse drug reaction terminology (WHO-ART).[2,13]

Management of adverse drug reactions was studied in terms of number and percentage of reactions that required suspected drug to be withdrawn or reduction in dose or no change in treatment.

Statistical Analysis

Statistical analysis was carried out by using statistical software IBM SPSS (version 21.0), MS excel 2010 and consultation with statistician.

Observations and Results

During the study period 157 patients were presented with ADRs due to antiretroviral drugs. Out of 157 patients presented with ADRs 131 (83.4%) reported their ADRs during their OPD visit while only 26 (16.6%) IPD patients reported ADRs. Total 223 ADRs were reported during the study.108 patients presented with single ADR (68.8%), 33 patients presented with 2 ADRs (21%), 15 presented with 3 ADRs (9.6%) and single patient presented with 4 ADRs due to HAART. Anemia (48, 21.5%) was the most common ADRs reported in this study, followed by Dizziness(39, 17.5%) Table 1.

Table 1: Adverse drug reactions reported due to HAART

Sr. No.	Name of ADRs	Frequency	Percentage
1	Anaemia	48	21.5
2	Neutropenia	2	0.8
3	Leucopenia	2	0.8
4	Reticulocytopenia	1	0.4
5	Dizziness	39	17.5
6	Giddiness	14	6.2
7	Psychosis	1	0.4
8	Insomnia	7	3.1
9	Somnolence	5	2.2
10	Headache	5	2.2
11	Abnormal dreams	8	3.5
12	Irritability	1	0.4
13	Anxiety	3	1.3
14	Nail discolouration	15	6.7
15	Rash	14	6.2
16	Itching	3	1.3
17	Fixed drug eruption	1	0.4
18	Skin hyperpigmentation	2	0.8
19	Palm hyperpigmentation	2	0.8
20	Steven Johnson syndrome	1	0.4
21	Nausea , Vomiting	15	6.7
22	Gastritis	5	2.2
23	Diarrhoea	2	0.8
24	Hepatomegaly	1	0.4
25	Raised liver enzyme	1	0.4
26	Hepatitis	1	0.4
27	Renal failure	7	3.1
28	Gynaecomastia	2	0.8
29	Peripheral Neuropathy	1	0.4
30	Myalgia	2	0.8
31	Lipodystrophy	2	0.8
32	Anorexia	4	1.7
33	Fatigue	2	0.8
34	Palpitation	2	0.8
35	Blurring of vision	2	0.8

Results of Demographic details, Risk factors and Presentation of ADRs

Out of 157 patients presented with ADRs, 106 (67.5%) were females and 51 (32.5%) were males. Mean weight of these patients was 45 kg (S.D. 11.5). Most common age group affected was 20-40 years which included 99 (63.1%) cases. As shown in the Table 2 females in age group 20-40 years [74, (47.1 %)] were most commonly affected.

Table 2: Age & Gender wise distribution of ADRs

Age in years		Gender			
		Male (%)		Female (%)	
Age group	<20	4	2.5	11	7
	20-40	25	16	74	47.1
	40-60	20	12.7	21	13.3
	>60	2	1.27	0	0
Total		51	32.47%	106	67.4%

As shown in Table 3 out of 157 patients presented with ADRs, most of them116 (73.9%) were from rural population while 41(26.1%) were from urban population. While 104 (66.2%) were literate and 53 (33.8%) were illiterate. In these study laborers 76(48.4%) were most commonly affected patients due to ADRs.

Table 3: Demographic details of patients presented ADRs

LOCALITY	**Frequency**	**Percentage**
Rural	116	73.9
Urban	41	26.1
Total	157	100.0
EDUCATIONAL STATUS	**Frequency**	**Percentage**
Literate	104	66.2
Illiterate	53	33.8
Total	157	100.0
OCCUPATION	**Frequency**	**Percentage**
Labourers	76	48.4
Truck Driver	8	5.1
Government Servant	8	5.1
Unemployed	8	5.1
House Wife	43	27.4
Skilled Worker	3	1.9
Student	8	5.1
Paediatric	3	1.9
Total	157	100.0

Relation between types of regimen and suspected ADRs

As shown in the Table 4, 86(54.8%) patients receiving Tenofovir, Lamivudine and Efavirenz (TLE) regimen were most commonly suffered from ADRs and the regimen was responsible for 135(60.6%) ADRs. Zidovudine, Lamivudine and Nevirapine (ZLN) containing regimen was the second most common regimen with 64 (40.8%) patients with ADRs. Few cases were also reported with regimens containing Zidovudine, Lamivudine and Efavirenz (ZLE) 6,(3.8%) patients . But only single case was reported with an ADR due to regimen containing Abacavir, Lamivudine and Efavirenz. (ALE).

Table 4: Relation between types of regimen and ADRs due to HAART

Types Of Regimen	**Patients presented with ADRs**	**Percentage**	**No. Of ADRs**	**Percentage**
TLE	86	54.8	135	60.6
ZLN	64	40.8	79	35.4
ZLE	6	3.8	8	3.6
ALE	1	0.6	1	0.4
Total	157	100	223	100

Table 5: Individual regimen wise ADRs

Sr. No	Name of ADR	ZLN	TLE	ZLE	ALE
1	Anemia	40	4	4	-
2	Dizziness	-	39	-	-
3	Nail discoloration	15	-	-	-
4	Nausea,Vomiting	1	13	-	1
5	Giddiness	-	13	1	-
6	Rash	8	6	-	
7	Abnormal dreams	-	8	-	-
8	Renal failure	-	7	-	-
9	Insomnia	-	7	-	-
10	Somnolence	-	5	-	-
11	Headache	-	5	-	-
12	Gastritis	-	5	-	-
13	Anorexia	-	4	-	-
14	Anxiety	-	3	-	-
15	Itching	2	1	-	-
16	Skin hyperpigmentation	2	-	-	-
17	Palm hyperpigmentation	2	-	-	-
18	Diarrhea		2		
19	Gynaecomastia	-	2	-	-
20	Myalgia		2		
21	Lipodystrophy	-	-	2	-
22	Fatigue	-	2	-	-
23	Palpitation	-	2	-	-
24	Blurring of vision	-	2	-	-
25	Irritability	-	1	-	-
26	Psychosis	-	1	-	-
27	Neutropenia	1	-	1	-
28	Leucopenia	1	-	1	-
29	Reticulocytopenia	1	-	-	-
30	Fixed drug eruption	1	-	-	-
31	Stevens-Johnson Syndrome	1	-	-	-
32	Hepatomegaly	1			
33	Raised liver enzyme	1			
34	Hepatitis	1			
35	Peripheral Neuropathy	-	1	-	-
	Total	79	135	8	1

II) Relation between CD4 count and occurrence of ADRs

In this study out of 157 patients developed ADRs due to HAART, 86 (54.8%) patients were presented with ADRs when their CD4 count at the time of occurrence of ADRs was more than 250/µl. Whereas 70 (44.6%) patients were presented at CD4 count less than 250/µl and CD4 count monitoring was not done in single patient. It shows that there is small difference between occurrence of ADRs and CD4 count at the time of ADRs. So we can't predict occurrence of ADRs due to HAART on the basis of CD4 count instead all the patients receiving HAART should be continuously observed for ADRs irrespective of their CD4 count.

III) Relation between occurrence of ADRs and Organ system affected

As shown in Table 6, out of total number of 223 ADRs, most of the patients were presented with one or more ADRs related with neurological system. So highest numbers of ADRs 64 (28.7%) were related with neurological system, followed by blood disorders 54 (24.2%) and skin and

appendages disorders 39 (17.5%). Gastrointestinal 25(11.2%), psychiatric 21(9.4%) and urinary tract related ADRs 7 (3.1%) were also commonly observed. Few patients also affected by ADRs related with most of the body system. So if patients receiving HAART present with some complaints related with commonly affected system by HAART then ADRs as cause of such complaints must be kept in mind.

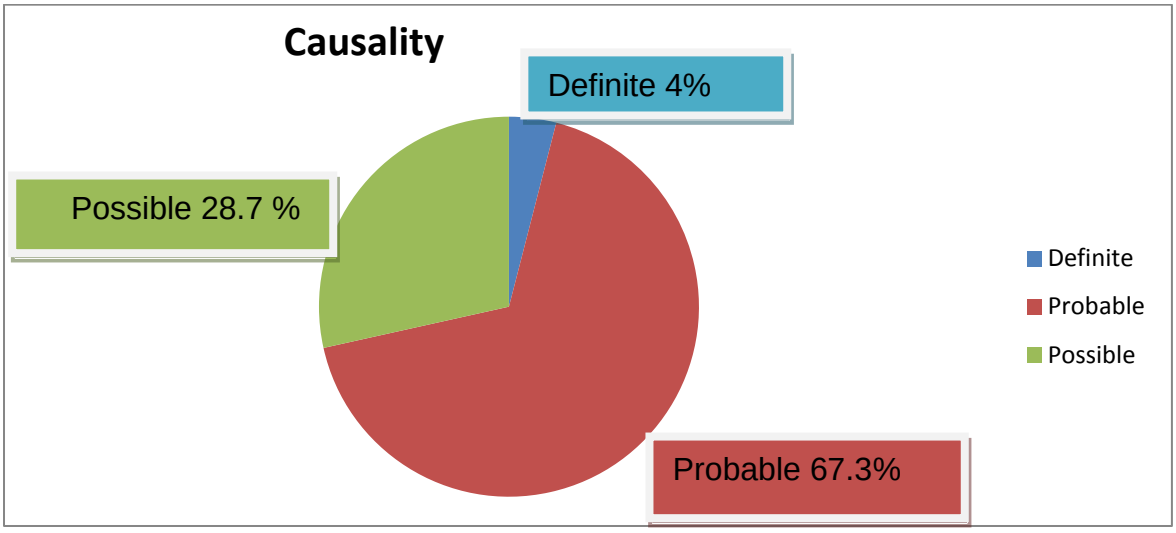
Table 6: Relation between numbers of ADRs organ system affected

Sr.No	Name of organ system affected	No. of ADRs	% of ADRs
1	Neurological disorder	64	28.7
2	Blood disorder	54	24.2
3	Skin and appendages disorder	39	17.5
4	Gastrointestinal disorder	25	11.2
5	Psychiatric disorder	21	9.4
6	Urinary tract disorder	7	3.1
7	Liver and biliary disorder	3	1.4
8	Cardiovascular disorder	2	0.9
9	Endocrine disorder	2	0.9
10	Vision disorder	2	0.9
11	Musculoskeletal disorder	2	0.9
12	Body as whole –General disorder	2	0.9
	TOTAL	223	100

2) Results of Causality assessment of ADRs

According to Naranjo's scale out of total number of 223 ADRs observed during the study, 150(67.3%) ADRs were probable, 64(28.7%) were possible and 9(4%) were having definite relationship with the suspected drugs (Figure 1).

Figure 1: Causality assessment of ADRs



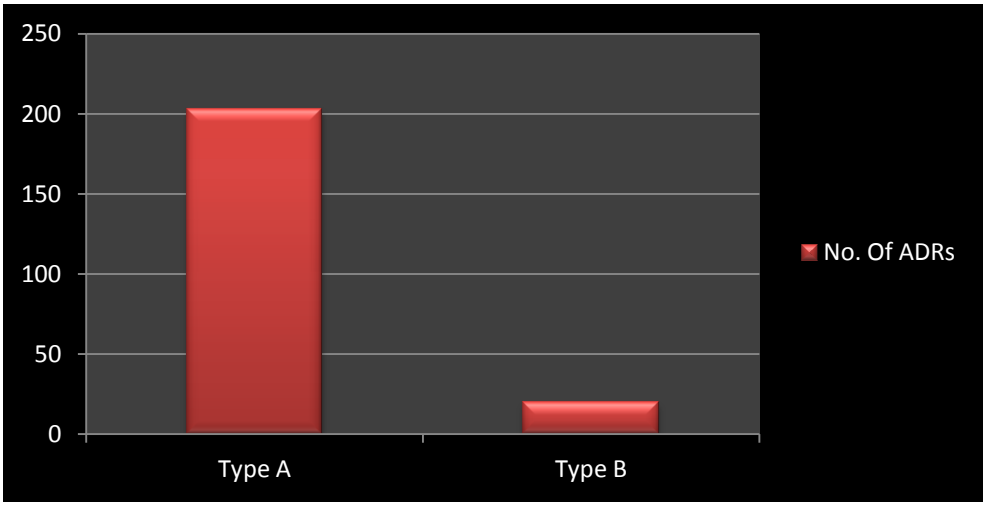
3) Results of classification and outcome of ADRs

A) Classification of ADRs

I) Rawlins and Thomson criteria of classification of ADRs

According to Rawlins and Thomson out of total number of 223 ADRs observed during this study most of the ADRs 203 (91%) were of Type- A while 20(9%) were of Type-B ADRs.

Graph1: Rawlins and Thomson Classification of ADRs



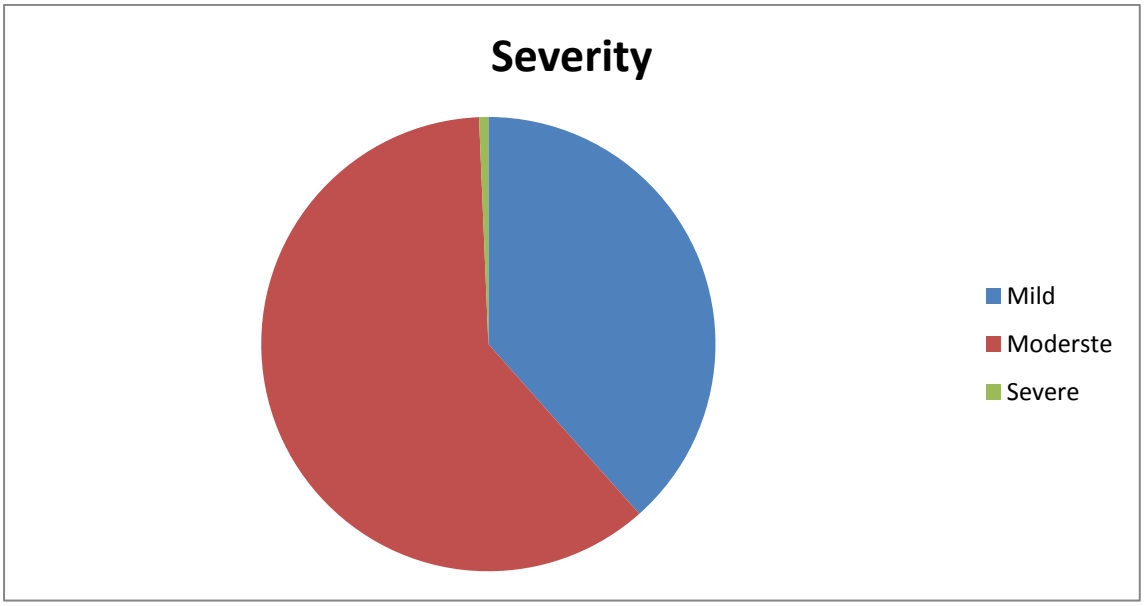
II) Classification based on seriousness of ADRs

In this study out of total number of 223 ADRs observed 61(27.4%) were serious type of ADRs while 162 (72.6%) were non serious type of ADRs.

III) Classification based on severity:

According to Hartwig's and Seigel scale for assessment of severity of ADRs, out of total number of 223 ADRs observed during this study, most of the ADRs(130,58.3%) were moderate in intensity, 82(36.8%) were mild type and 11(4.9%) ADRs were of severe type of ADRs

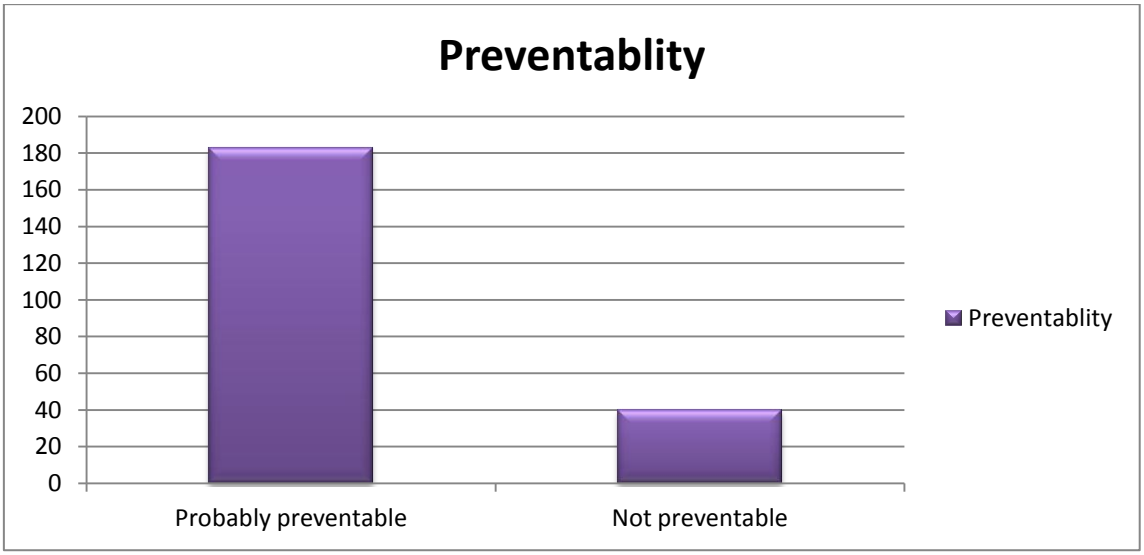
Figure 2: Severity of ADRs



IV) Classification based on Preventability of ADRs

As shown in Graph 2, according to Modified Shumock and Thornton scale for assessment of preventability of ADRs, out of total number of 223 ADRs, 183(82.1%) ADRs observed in this study were probably preventable and 40(17.9%) were not preventable.

Graph 2: Preventability of ADRs



B) Outcome of ADRs

I) Management of ADRs

The management of ADRs due to HAART showed that out of 223 ADRs reported during this study, 118(52.9%) ADRs required withdrawal of suspected drugs, 4(1.8%) required reduction in dose while 101(45.3%) of ADRs required no change in the suspected drugs causing ADRs.

II) Outcome of ADRs

Out of 223 ADRs reported during this study, most of ADRs 180(80.8%) were recovered, 4(1.8%) were recovering, 21(9.4%) were continuing and 3 (1.3%) reactions were fatal. But outcome of 15(8.7%) ADRs were not known because these patients were either referred to other center or lost to follow up.

Discussion

Acquired immunodeficiency syndrome is global health related problem. Many drugs have been approved for treatment of HIV that leads to reduction in morbidity and mortality but the adverse effects of HAART made the treatment more complicated.

There is deficiency of awareness about drug safety monitoring among health care professionals.[2] Monitoring and reporting of ADRs due to HAART is very important measure to prepare new guidelines to improve quality of life of patients.

Out of 157 patients presented with ADRs during this study 106(67.5%) were females and 51 (32.5%) were males. Females in the age group 20-40 years were commonly affected which is same as the finding of the study conducted by Obiako etal.[5] Another study conducted by Singh and et al also showed that female patients had more ADRs than males.[14]The exact reasons for sex differences in adverse reactions to antiretroviral drugs is unknown. Several studies in human pharmacologyhave described differences in pharmacokinetics, in drug response toxicity between males and females. Differences in weight and body mass index between men and women may be playing an important role.

Assessment of other demographic parameters in our study showed that laborers (48.4%) residing in rural (73.9%) area were more commonly affected due to ADRs (Table 3). In this study literate people (66.2%) reported more ADRs than illiterate which showed the lack of knowledge and awareness of illiterate people regarding reporting of ADRs.

In our study, maximum ADRs occurred in patients receiving TLE which was commonly prescribed regimen in these patients but anemia (21.5%) suspected due to Zidovudine containing regimens (ZLN and ZLE) was the most common ADR reported in this study (Table 4 and 5). A study from Karnataka also showed anemia as most

common ADRs due to HAART therapy.[6] Finding of study conducted by Sharma and et al was different from our study in which cutaneous ADRs were most common ADRs (44.4%).[15] Zidovudine one of the highly effective antiretroviral drug which is also associated with side effects mainly myelosupression, manifesting clinically as anemia.

Neuropsychiatric adverse effects were reported with Efavirenz therapy. These symptoms include dizziness, giddiness, abnormal dreams, insomnia, drowsiness, headache and psychosis. In our study highest numbers of ADRs (85, 38.11%) were related to neuropsychiatric system. Another study also showed that CNS adverse reactions were reported to be very common in EFV containing regimens. A study confirms multiple EEG abnormalities in Efavirenz treated patients with difficulty in sleeping and correlated with serum drug levels.[16] In this study most of ADRs were related with neuropsychiatric system because of TLE was the most commonly prescribed regimen in our institute and most common ADR ssuspected due to Efavirenz which was similar to findings of study done by Reddy et al.[17]

The Naranjo's algorithm is widely used in causality assessment of ADRs. In our study most of the ADRs 150(67.3%) were probable, 64 (28.7%) were possible and 9 (4%) were having definite relationship with the suspected drugs. Our finding differs with those of study done by Bhuvana et al where majority of ADRs were found to be possible.[6] In our study some definite type of ADRs were also reported because some patients receiving TLE stopped their regimens due to some adverse effect and restarted by themselves and develop the same ADRs.

According to modified Shumock and Thornton criteria used for assessment of preventability most of the ADRs 183(82.1%) were of probably preventable type and only 40(17.9%) were not preventable (Graph 2).This shows that most of the ADRs due to HAART therapy were preventable. Proper counseling of patients, starting drugs at low doses, iron supplementation and regular hemoglobin checkup can helps to prevent these ADRs and to improve compliance of patients.

During this pharmacovigilance study we observed that 157 patients receiving HAART presented with 223 different ADRs affecting various body system. The high incidence of anemia in patients receiving Zidovudine containing regimen was consistent with other studies.[6],[18] The high incidence of neuropsychiatric ADRs dueto Efavirenz and renal failure due to Tenofovir was striking finding in our study. So TLE based ART warrants rethinking of the guidelines to combat these ADRs and to increase adherence of the patients. So this study proves that there is further need of such pharmacoviglance study for continuous monitoring of ADRs due to antiretroviral drugs which will help to prepare more effective ART guidelines.

Conclusion

This pharmacovigilance study of antiretroviral drugs concludes that the risk factors for development of ADRs were gender female, age group 20-40 years, occupation labor in rural area taking ZLN and TLE regimens. In this study anemia due to Zidovudine containing regimens was the most common ADR followed by dizziness due to Efavirenz containing regimen.

The ADRs assessed in this study were of probable, type A, nonserious, mild to moderate in severity and probably preventable. Most of these ADRs recovered with or without change in suspected drugs.

From this study we suggest that there is need of continuous monitoring of ADRs with antiretroviral drugs which will help to identify the risk factors related with ADRs and to prepare new guidelines for treatment and prevention of ADRs.

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Declaration
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Conflict of interest: None declared.
Ethical approval: The study was approved by the Institutional Ethics Committee

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