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Research Article

PHARMACOVIGILANCE STUDY OF ANTIRETROVIRAL THERAPY IN HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME PATIENTS AT ANTIRETROVIRAL THERAPY CENTRE, JABALPUR

RAJKUMARI BANSAL, DARYANI K K, AJIT PRATAP SINGH*

Department of Pharmacology, NSCB Medical College Jabalpur, Madhya Pradesh, India. Email: drajitsingh1978@gmail.com

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ABSTRACT

Objective: The objective of the study was to assess the adverse drug reactions (ADRs) of antiretroviral therapy along with its causality, severity, and preventability.

Method: A prospective as well as a retrospective observational study with a sample size of 260, jointly conducted in the Department of Pharmacology and antiretroviral therapy (ART) center of N.S.C.B. Medical College Jabalpur, India, from March 2016 to July 2017. We observed various ADRs to ART in human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients and assessed causality, severity, and preventability of the reported ADRs as per the standard scales.

Results: A total of 260 patients were enrolled of which 220 (84.6%) patients developed a total of 425 ADRs. Maximum 51.7% of ADRs were caused by TLE followed by 37% with ZLN regimen. Most common ADRs were dizziness 18.6%, rashes 14.6%, anemia 10.6%, and vomiting 6.6%. Dizziness and rashes are mainly caused by TLE and ZLN regimen, respectively. Management of ADRs with a change in the regimen was applied as an interventional tool in 40% of the patients. Causality assessment as per the WHO-UMC scale showed that 55.5% of ADR were probable and 45.5% were possible. 84.5% of ADR was not preventable, while 15.5% of ADRs were probably preventable. 38% of ADRs were mild, 56% were moderate, and 6% were severe in nature.

Conclusion: Antiretrovirals, however, the milestone for the treatment of HIV/AIDS have very high potential for developing ADRs. Hence, active pharmacovigilance is needed for not only safety of the patients but also compliance to the treatment which is necessary for optimal therapeutic outcomes and to improve quality of life.

Keywords: Pharmacovigilance, Adverse drug reaction, Antiretroviral therapy, Acquired immunodeficiency syndrome.

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INTRODUCTION

The word "pharmacovigilance (PV)" is derived from pharmakon (Greek: Drug) and vigilare (Latin: To keep watch) also known as drug safety, refers to the process of continuous monitoring for unwanted effects and other safety-related aspects of marketed drugs [1]. PV heavily focuses on adverse drug reactions (ADRs), which is defined by the WHO as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [2]. The thalidomide disaster, detected in 1961, is a milestone in origin and further development of PV. The WHO started a program for international drug monitoring in 1968. The Uppsala Monitoring Centre (UMC) was established in 1978 to support the WHO Programme for International Drug Monitoring. At present, 134 countries are participating in the PV program which is centrally coordinated by the WHO with its collaborating centre in Uppsala, Sweden. The UMC (UMC, WHO) maintains the global ADR database which contains more than 12 million reports in the software "Vigibase," a web-based online system [3].

Monitoring of ADRs is especially important when treatment is being scaled up, such as antiretroviral therapy (ART) for the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) patients. Although ART is very effective, these drugs are highly toxic and are associated with various ADRs; therefore, many patients warrant withdrawal of the drugs or even discontinuation of treatment resulting in treatment failure. Hence, PV plays an important role in the management of treatment and ensuring safety in HIV patients [4].

AIDS is a global problem. It has now been reported from more than 190 countries around the world, and a pool of HIV infected persons in Africa and Asia is large and expanding. Since the start of the epidemic, an estimated 76.1 million people have become infected with HIV, and 35 million people have died of AIDS-related illnesses. In only 2016, 1 million people died from AIDS-related illnesses, and 1.8 million people became newly infected worldwide. According to the UNAIDS, about 36.7 million people were living with HIV globally by the end of 2016. Among them, 19.5 million people have access to ART [5].

The world has committed to end the AIDS epidemic by 2030. UNAIDS recommends a Fast-Track approach to achieve the 90–90–90 treatment target by 2020, whereby 90% of people living with HIV should know their HIV status, 90% of people who know their HIV-positive status are accessing treatment, and 90% of people on treatment have suppressed viral loads. Global consensus and leadership have driven greater investment of financial and human capital, and mounting clinical experience and research, improved treatment regimens and diagnostics and reductions in the price of medicines have created gains in efficiency and effectiveness [6].

In India, approximately 2.1 million people are living with HIV in 2016, which is estimated to be the third largest population of HIV affected people in the world. In 2016, HIV prevalence in India was estimated at 0.3%, and 62,000 people died from AIDS-related illnesses. Estimated numbers of new HIV infections in 2016 were 80 thousand and 1 million people are on ART who are living with HIV. The number of people newly initiating ART in 2016 was 176969 [7].

Growing socioeconomic burden of the disease in India led to the inception of National AIDS Control Organization (NACO) in 1986 and subsequently in the formation of National AIDS Programme in 1987. ART became the keystone of National AIDS Programme [8].

ART involves a combination of at least three or more HIV medicines from at least two classes of antiretroviral agents called highly active ART refer to as Anti-HIV "cocktail," given to the patients every day. It can slow the disease progression by preventing the virus from multiplying and destroying the CD4 cells, thus decreases the amount of virus in an infected persons' blood (viral load) and restore the immune system [9].

There are mainly six major classes of antiretroviral agents:
1. Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs) - zidovudine, abacavir, didanosine, emtricitabine, lamivudine, stavudine, and tenofovir.
2. Non-nucleoside reverse transcriptase inhibitors - efavirenz and nevirapine.
3. Protease inhibitors - atazanavir, lopinavir, and ritonavir.
4. Integrase inhibitors - raltegravir.
5. Fusion inhibitors - enfuvirtide.
6. Chemokine receptor antagonists (CCR5 antagonists) - Maraviroc.

There is also a medicine called cobicistat which increases the action of antiretrovirals but does not have any effect on the virus itself. Each drug class disrupts different stages of viral life cycle [10]. The documented side effects of these drugs are: Zidovudine causes bone marrow suppression leading to anemia and neutropenia. Stavudine causes nausea, peripheral neuropathy, pancreatitis, and lipoatrophy. Nevirapine causes skin rash, Steven Johnson Syndrome (SJS) and hepatitis. Efavirenz causes skin rash in 10% of patients. Lamivudine has minimum toxicity. Most common adverse effects of lamivudine were diarrhea, malaise, fatigue, headache, and sleep disturbances [11]. In our study, we observed the various ADRs to ART in HIV/AIDS patients and assessed causality, severity, and preventability of the reported ADRs at ART center Netaji Subhash Chandra Bose Medical College, Jabalpur M.P.

METHODS

After approval from the Institutional Ethics Committee, the study was jointly conducted in the Department of Pharmacology and ART center of N.S.C.B. Medical College, Jabalpur (MP), from March 2016 to July 2017. It was a prospective as well as a retrospective observational study with a sample size of 260. The participants had been offered to voluntarily participate in the study. They had given written informed consent before they were enrolled in the study.

Inclusion Criteria

The following criteria were included in this study:
1. Patients of any age of either sex.
2. Both new and old registered patients who were on ART.
3. Patients who gave written informed consent.

Exclusion Criteria

The following criteria were excluded from this study:
1. Patients who do not give informed consent for participation in the study.
2. Patients who were not able to recall or explain the symptoms of ADR.
3. Patients unable to respond to verbal questions.

Every enrolled patient who was already on ART and who has newly started the ART during this study period, were observed. These patients were provided with Informed Consent Form, and their consent for the study was documented. Details of the participants were kept confidential. Detailed history of the patient including demographic detail, past and present illness, and concurrent systemic illness, and drug history was taken along with detailed clinical examination when the patient came for follow-up visits to ART center. These informations were recorded on a pre-designed patient pro forma and correlated with prefilled patient treatment records (white card). Essential laboratory investigations such as complete blood counts, liver function tests, renal function tests, lipid profile, blood sugar tests, and CD4 count were done or recorded from prefilled patient treatment records.

All the ADRs were duly filled up in the suspected adverse drug reaction reporting form of Central Drugs Standard Control Organization by interviewing with patient or patients' caretaker and by reviewing prefilled patient treatment records. To establish the etiologic agents for ADR, attention was paid to the drug history, speculating the temporal correlation with the drug, duration of ADR, type of reaction, improvement in reaction on withdrawal of drug and recurrence of reaction on rechallenge if possible. These ADR was further assessed for its causality, preventability, and severity using WHO-UMC criteria [12], Modified Schumock and Thornton criteria [13], and Modified Hartwig and Siegel scale [14], respectively. The data were analyzed using SPSS 20. Appropriate univariate and bivariate statistical analysis was carried out using the student's *t*-test for the continuous variable (age) and two-tailed Fisher exact test or Chi-square (χ^2) test for categorical variables. All means are expressed as mean ± standard deviation and proportion in percentages. The critical levels of significance of the results were considered at 0.05 levels, i.e., $p<0.05$ was considered significant.

RESULTS

A total of 260 patients were enrolled in our study in which 47.7% were males and 52.3% females. Only 220 (84.6%) patients developed ADRs among them 47.3% were males and 52.7% were females. A total of 425 ADRs were observed of which 41% occurred in males and 59% in females (Table 1). Majority 68.2% of the cases was observed in 21–40 years in ADR+ group followed by 22.3% in 41–60 years in the same. The mean age of cases in ADR+ group was observed to be 34.06 (±11.12) years. Statistically, cases with ADR belonged to significantly higher ($p<0.001$) mean age (Table 2). 45% and 38.6% of patients who experience ADRs were on regimen TLE and ZLN, respectively. Maximum 51.7% of ADRs were caused by TLE followed by 37% with ZLN regimen (Table 3).

Table 1: Gender distribution

Gender	Total n=260 (%)	ADR+n = 220 (%)	Total ADRs n=425 (%)
Male	124 (47.7)	104 (47.3)	174 (41)
Female	136 (52.3)	116 (52.7)	251 (59)

χ^2=0.10; P>0.05 at 1df, ADRs: Adverse drug reactions

Table 2: Age distribution

Age (years)	Total n=260 (%)	ADR+n = 220 (%)	Total ADRs n=425 (%)
0–20	24 (9.2)	17 (7.7)	28 (6.6)
21–40	179 (69)	150 (68.2)	298 (70.1)
41–60	53 (20.3)	49 (22.3)	86 (20.2)
>60	4 (1.5)	4 (1.8)	13 (3.1)
Mean±SD	33.09±11.236	34.06±11.123	

t=3.33; P<0.001, ADRs: Adverse drug reactions

Table 3: Drug regimens and patients found with ADRs

Regimen	Total patients n=260 (%)	ADR (+) patients n=220 (%)	Total ADRs n=425 (%)
ALN	8 (3.1)	7 (3.2)	8 (1.9)
SLN	21 (8.1)	17 (7.7)	22 (5.2)
TLE	121 (46.5)	99 (45)	220 (51.7)
TLN	8 (3.1)	7 (3.2)	10 (2.3)
ZLE	5 (1.9)	5 (2.3)	8 (1.9)
ZLN	97 (37.3)	85 (38.6)	157 (37)

χ^2=2.63; P>0.05 at 5df, ADRs: Adverse drug reactions

Most common ADRs were dizziness 18.6%, rashes 14.6%, anemia 10.6%, and vomiting 6.6%. Dizziness and rashes are mainly caused by TLE and ZLN, respectively. Nightmares 2.6% and renal toxicity 3.3% are found only in TLE. Lipodystrophy 1.4% occurred by SLN and TLE. Anemia 10.6% and neutropenia 3.3% mainly occurred in ZLN. Excessive sweating 0.9% and hair fall 1.4% occurred in TLE and ZLN, respectively. Only 2 patients had SJS, in ZLN (Table 4).

Table 5 shows interventions taken after experiencing ADR by different regimens. 2.3% patients of SLN and 8.6% patients of ZLN were switched to SLE and ZLE regimen, respectively. 7.3% patients were switch to SLN who were on ZLN regimen. 15% of patients were allowed to withhold the treatment. Thus, the change in the regimen was applied as an interventional tool in 40% of the patients to alleviate there ADRs.

Causality assessment as per the WHO-UMC causality scale shows that 98 (44.5%) patients, among a total of 220, had possible affiliation to the offending drug while 122 (55.5%) patients had a probable association to the drugs (Table 6). Preventability assessment according to modified Schumock and Thornton scale shows that of 220 patients who were found to have ADRs in our study, 186 (84.5%) patients would not be prevented while 34 (15.5%) patients would probably be prevented (Table 7). Table 8 shows that majority of patients were categorized in to mild and moderate in terms of severity assessment of ADR's using modified Hartwig and Siegel scale.

DISCUSSION

A total of 260 patients were observed during the study period of 18 months. Patients developed ADRs with the incidence rate of 84.6%. Sharma *et al*. [15] found the incidence rate of 71.1% which was less than ours whereas Nagpal *et al*. [16] reported that 90.64% patients experienced ADRs which were higher as compared to our study. Our study showed a higher prevalence of ADR in female (52.7%) than male (47.3%). Similar finding was also reported by Sadiq *et al*. [17], with a higher prevalence in female (64%) as compared to male (36%). In contrast, Khan *et al*. [18] reported a higher prevalence of ADRs in male (74.8%) than female (25.2%). The factors of the gender differences

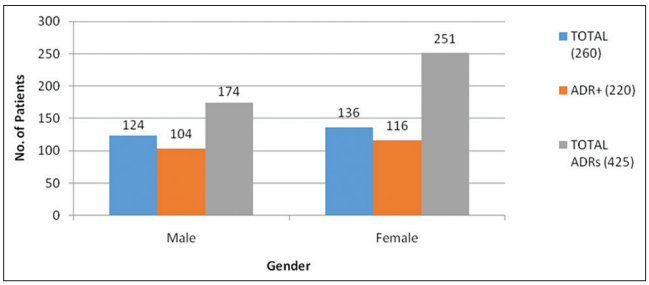

Fig. 1: Gender distribution

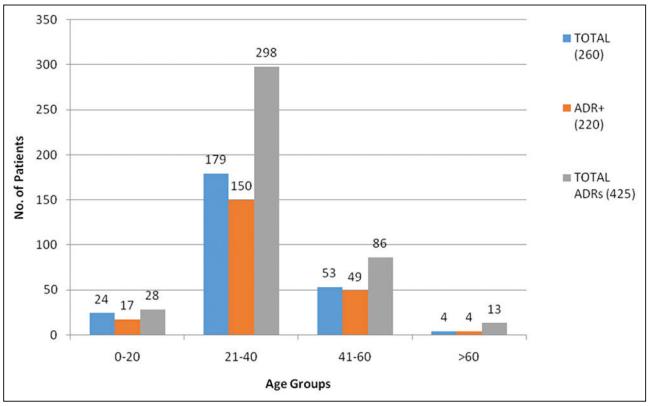

Fig. 2: Age distribution

Table 4: Various ADRs among different regimens

System	ADR	ALN (n=8)	SLN (n=22)	TLE (n=220)	TLN (n=10)	ZLE (n=8)	ZLN (n=157)	Total ADR (n=425) [%]
CNS	Depression			6				6 (1.4)
	Dizziness		1	70	1		7	79 (18.6)
	Drowsiness			8				8 (1.9)
	Headache			7			5	12 (2.8)
	Insomnia			9				9 (2.1)
	Neuropathy		5	3			1	9 (2.1)
	Nightmares			11				11 (2.6)
	Psychosis			5			1	6 (1.4)
	Suicidal tendency			2				2 (0.5)
GIT	Anorexia			9		1	9	19 (4.5)
	Diarrhea			1			2	3 (0.7)
	Gastritis			4			2	6 (1.4)
	Nausea		1	11			8	20 (4.7)
	Pancreatitis			1		1		2 (0.5)
	Vomiting		1	18			9	28 (6.6)
Hepatorenal	Jaundice		1				5	6 (1.4)
	Renal toxicity			14				14 (3.3)
Dermatological	Excessive sweating			4				4 (0.9)
	Hair fall						6	6 (1.4)
	Hyper Pigmentation			2			3	5 (1.2)
	Itching			4	2		6	12 (2.8)
	Rashes	7	9	8	6		32	62 (14.6)
	Steven-Johnson Syndrome						2	2 (0.5)
Hematological	Anemia	1				4	40	45 (10.6)
	Neutropenia					2	12	14 (3.3)
Others	Fatigue			12	1		4	17 (4.0)
	Fever		1	3				4 (0.9)
	Giddiness			1			2	3 (0.7)
	Lipodystrophy		3	3				6 (1.4)
	Myalgia			4			1	5 (1.2)

ADRs: Adverse drug reactions, CNS: Central nervous system

Table 5: Interventions after ADRs

Interventions after ADRs	Previous regimens						Total n=220 (%)
	ALN (n=7)	SLN (n=17)	TLE (n=99)	TLN (n=7)	ZLE (n=5)	ZLN (n=85)	
Switch to SLE		5					5 (2.3)
Switch to SLN						16	16 (7.3)
Switch to TLE	1	9		6	3	29	48 (21.8)
Switch to ZLE						19	19 (8.6)
Counseling (Couns.)			45	1			46 (21)
Counseling with Symp. t/t		1	40			12	53 (24)
Withhold	6	2	14		2	9	33 (15)

ADRs: Adverse drug reactions

Table 6: Causality assessment

Causality assessment	Number of patients n=220 (%)
Possible	98 (44.5)
Probable	122 (55.5)

Table 7: Preventability assessment

Preventability assessment	Number of patients n=220 (%)
Not preventable	186 (84.5)
Probably preventable	34 (15.5)

Table 8: Severity assessment

Severity assessment	Number of patients n=220 (%)
Mild	84 (38)
Moderate	123 (56)
Severe	13 (6)

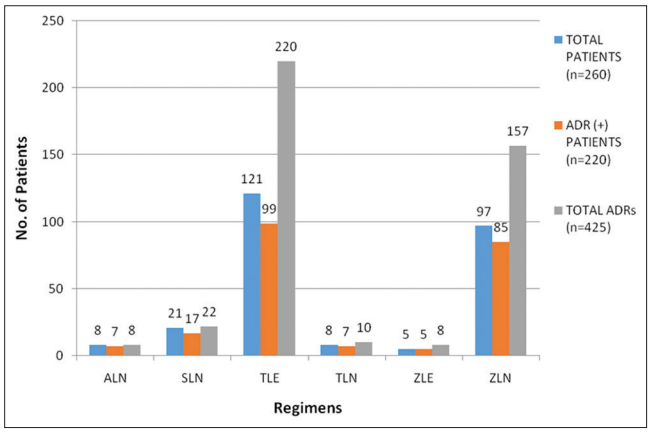

Fig. 3: Drug regimens and patients found with adverse drug reactions

for the appearance of ADRs might be due to hormonal effects, drug metabolism, fat composition, body mass index, immunological status, environmental factor, or genetic constitutional differences at the level of various enzymes.

Majority of the patients (69%) belong to the age group of 21–40 years followed by the group between ages 41 and 60 years (20.3%). This is comparable to the study of Sehgal *et al.* [19] who found that a large number of patients (74.9%) belongs to the same age group.

Of total 425 ADRs, 51.7% occurred in patients who were on TLE regimen, 37% in the patients on ZLN regimen and remaining by others regimens. This is in accordance with Kumar *et al.* [20] where maximum ADRs amounting to 49.23% and 23.85% were observed with patients on TLE and ZLN regimen, respectively.

Most common ADR observed was dizziness 18.6%, rashes 14.6%, anemia 10.6%, vomiting 6.6%, and nausea 4.7% in our study. Jain *et al.* [21] also found dizziness 22.6% to be the most common ADR. Similar findings were also observed by Sehgal *et al.* [19]where dizziness was the most common central nervous system (CNS) adverse effect while Singh *et al.* [22] found peripheral neuropathy (20.8%) as the most common ADR in their study. Other CNS ADRs were headache 2.8%, nightmares 2.6%, insomnia 2.1%, neuropathy 2.1%, drowsiness 1.9%, psychosis 1.4%, depression 1.4%, and suicidal tendencies 0.5% as observed in our study which is caused by TLE regimen except for neuropathy which occurred mainly due to SLN regimen. This is in concordance with the study of Nagpal *et al.* [16]and Reddy *et al.* [23]. We found that efavirenz is commonly associated with CNS ADRs as observed by Sehgal *et al.* [19] and Kumar *et al.* [20]. This is mainly because of the hydroxylation of efavirenz to 8-hydroxy efavirenz, through CYP2B6, which is the main metabolite causing CNS toxicity. Acute psychosis and suicidal tendency were reported as new ADRs in our study. One case of these was found to be as severely life-threatening, and remaining 5 were moderate in nature. It is very difficult to distinguish whether they are due to newly diagnosed disease origin or induced due to drug therapy. In such cases, we need psychiatric intervention. Mild to moderate cases of neuropathy were reported as tingling, numbness or paresthesia and in severe form permanent nerve damage due to stavudine-based regimens. We observed mild to moderate cases of neuropathy. As an intervention in peripheral neuropathy, we changed the regime and gave symptomatic treatment in the form of multivitamins. Newly started TLE causes dizziness as the most common side effect which subsided after 3–4 weeks with the regime being continued. The patient can be managed alone by counseling or assurance.

Vomiting 6.6%, nausea 4.7%, and anorexia 4.5% were the most common gastrointestinal ADRs followed by gastritis 1.4%, diarrhea 0.7%, and pancreatitis 0.5% in our study. 42.4% ADRs were gastrointestinal among all reported ADRs by Nagpal *et al.* [16] which comprised anorexia 24.8%, gastritis 14.1%, diarrhea 11.8%, nausea 7.2%, and vomiting 6.5%. Khan *et al.* [18] observed pancreatitis 3.1%, diarrhea 1.4%, and vomiting 0.7% in their study. Sharma *et al.* [15] observed gastritis 10%, anorexia 1.1%, diarrhea 1.1%, and pancreatitis 1.1% in their study. Reddy *et al.* [23] also reported the most common ADR in their study to be gastrointestinal with gastritis 13.13%, anorexia 6.8%, and nausea 2.5%. In our study, most of GIT side effects are caused by TLE and ZLN regimen. This is in concordance with Kumari *et al.* [24] who found that maximum gastrointestinal ADRs occurred with TLE and ZLN regimen.

Nearly 1.4% of ADRs reported were jaundice and renal toxicity to be having an incidence of 3.3%. Weldegebreal *et al.* [25]reported jaundice to be at 1.6% which was comparable to our study. Rather *et al.* [26] found renal toxicity (elevated serum creatinine) to be 3% which was also comparable to our study. Jaundice as nonspecific ADR can cause by all type of regimens but in our study mostly caused by ZLN and SLN (attributed to nevirapine) which appear in the form of the increased liver enzyme. In severe cases, elevated liver enzyme can rise to 5 times.

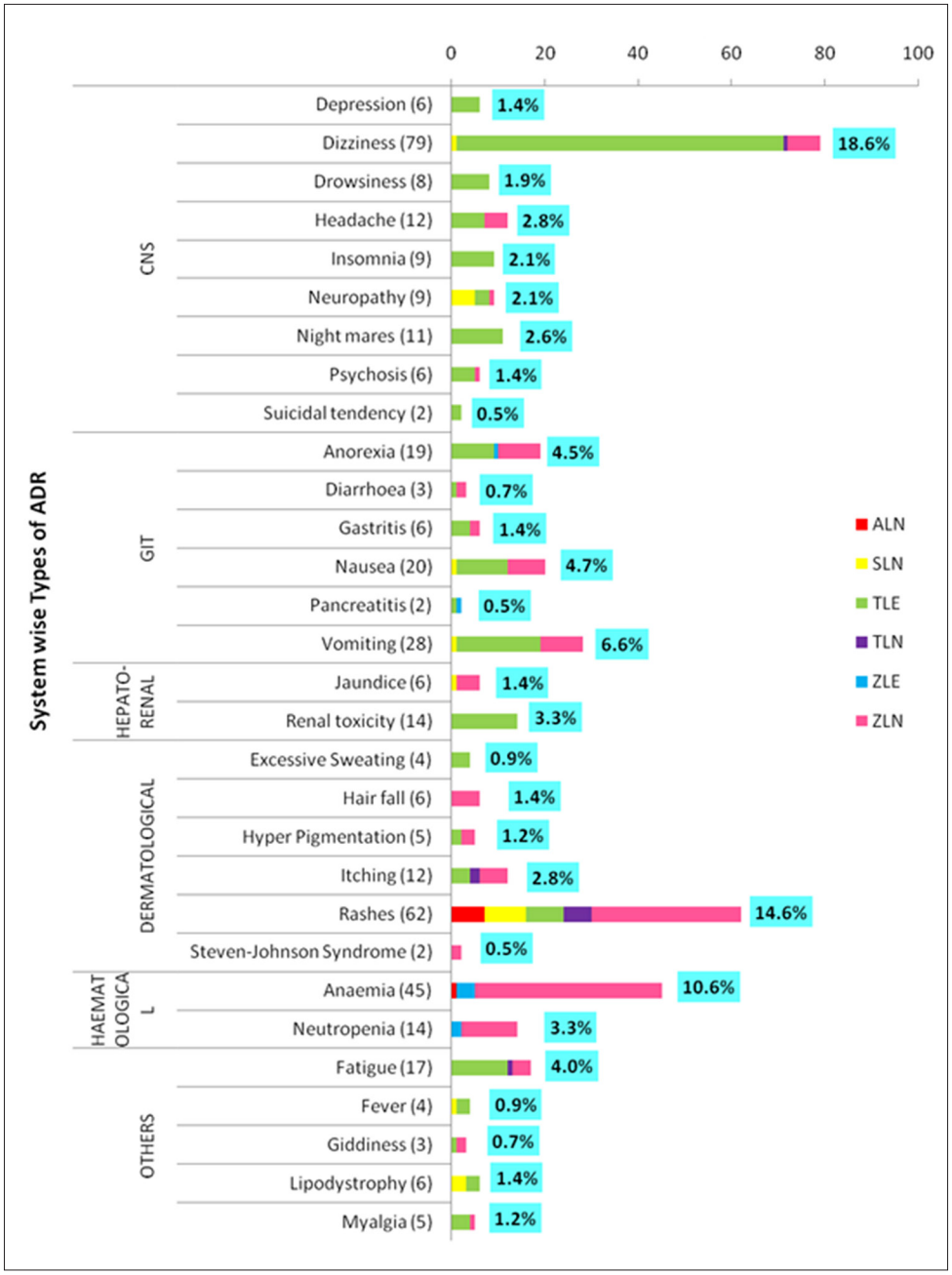

Fig. 4: Various adverse drug reactions among different regimens

Such cases want withholding the treatment until full recovery and restart an alternative therapy with close monitoring. Weldegebreal *et al*. [25] were in support of our observation where jaundice was caused by zidovudine-based regimen. Rather *et al*. [26] correlated hepatitis due to NRTIs which were also similar to our results. Renal toxicity was found mainly in TLE/tenofovir-based regimen which is concordance to Kumar *et al*. [20]. It is in the form of raised serum creatinine, increased uric acid or reduced creatinine clearance. When it occurs, therapy has to be withdrawn up to full recovery and adjustment of doses as per creatinine clearance.

It is a challenging task for the treating physician to distinguish whether the symptoms are due to the illness itself or through the drugs, however on withdrawing the drug if symptoms subside or resolve then it is in the favor of drug-induced reaction while if the symptoms worsen then it may be due to the illness itself.

Among dermatological reactions, rash 14.6%, itching 2.8%, hair fall 1.4%, hyperpigmentation 1.2%, excessive sweating 0.9%, and SJS 0.5%, were observed in our study. Masenyetse *et al*. [27] found the incidence of rash to be at 15% which is similar to our finding. Hyperpigmentation 14.4%, itching 7.7%, SJS 3.3%, and hair loss 2.2% were found in the study by Sharma *et al*. [15] which is in support of our study. In our study, dermatological ADRs were mostly associated with ZLN regimen which is in concordance with Sharma *et al*. [15] and Reddy *et al*. [23] who also found that most of the cutaneous ADRs were due to ZLN regimen.

In our study, five cases of rashes were mild in nature and some of which are associated with itching. They occurred with the initiation of therapy and subsided after 1–2 weeks with symptomatic treatment. 20 cases were moderate to severe in nature which was managed by a change in the regimen and or withholding the treatment. Most of the rashes were maculopapular in type which is caused mainly by nevirapine,

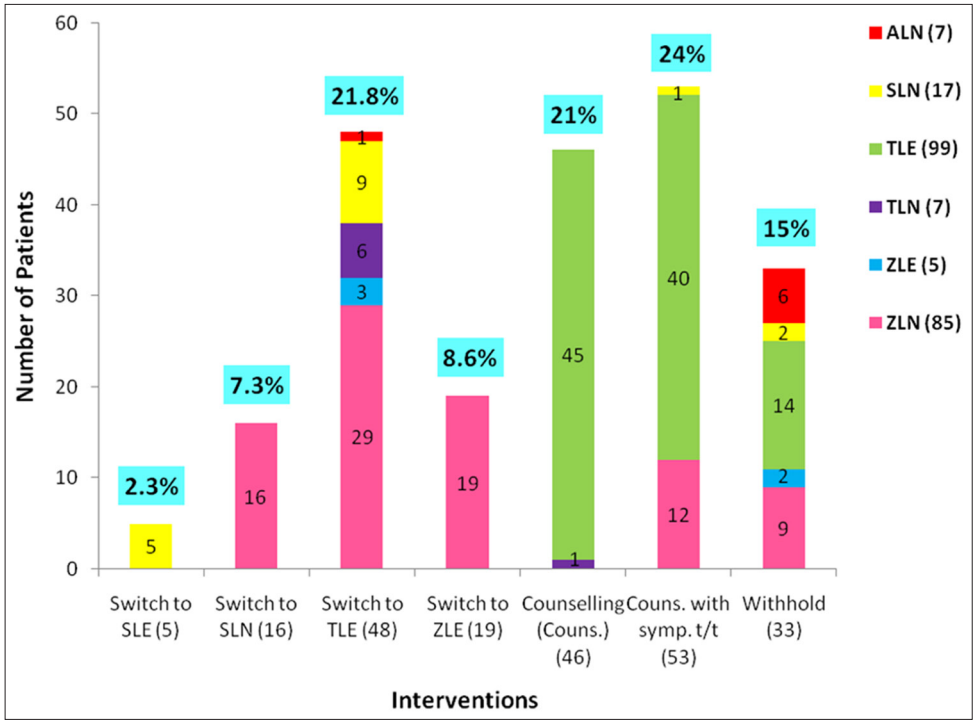

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Fig. 5: Interventions after adverse drug reactions

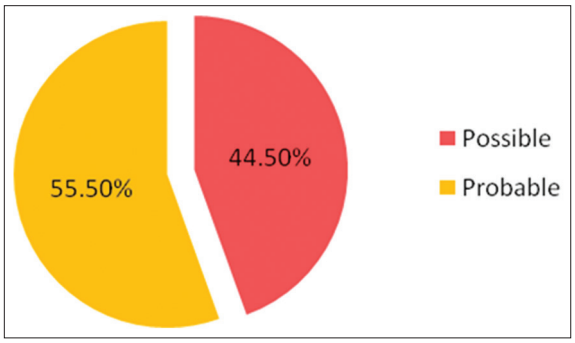

Fig. 6: Causality assessment

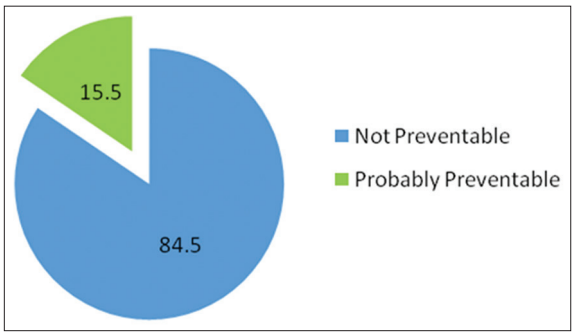

Fig. 7: Preventability assessment

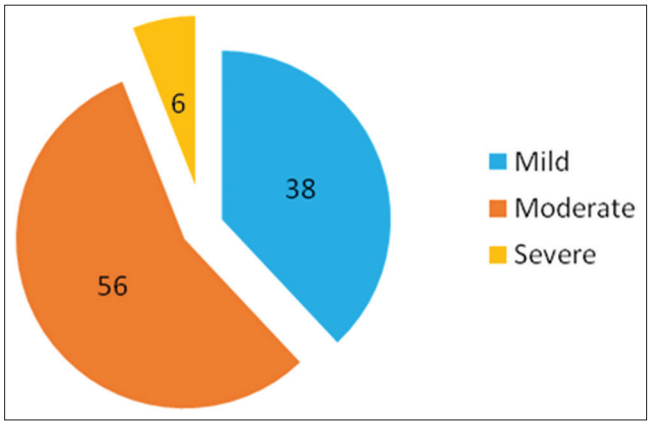

Fig. 8: Severity assessment

Rather *et al.* [26] were too in concordance with our study who also found rashes to be caused by nevirapine while Weldegebreal *et al.* [25] observed skin rashes with zidovudine- and tenofovir-based regimen. Two cases of Steven-Johnson Syndrome were reported which required intensive care. It was very severe in form with generalized bulbous eruptions, mainly due to ZLN regimen and required withholding the therapy until full recovery and further switching to another therapy. Sharma *et al.* [15] and Reddy *et al.* [23] also showed the occurrence of rash to be caused by nevirapine-containing regimen.

Hematological ADRs, mostly due to zidovudine-based regimen, were anemia 10.6% and neutropenia 3.3%. Zidovudine causes bone marrow suppression which is the main factor for its causing anemia and neutropenia. Rather *et al.* [26] were too in supports to our study, where they observed anemia 58.6% and neutropenia 11.1% as the hematologic ADRs occurring with the zidovudine-based regimen. Three cases of severe anemia were reported with the hemoglobin of <5 g% and remaining cases under moderate anemia with the hemoglobin range of 6–8 g%. Only three cases required withhold of treatment, and remaining were changed to another therapy with hematinics or blood transfusion. Abdissa *et al.* [28]are also in accordance to our study who found severe toxicities as anemia 32% and neutropenia 29.5% in their study.

Others ADRs such as fatigue 4%, lipodystrophy 1.4%, myalgia 1.2%, fever 0.9%, and giddiness 0.7% were also reported in our study. Sadiq *et al.* [17] and Reddy *et al.* [23] found similar types of ADRs in their studies.

Patients who experienced ADRs were managed by switching one drug or whole regimen (40%). Patients who developed severe ADRs were

allowed to withhold (15%) the treatment until full recovery. Majority of mild to moderate cases of ADR were managed by counseling (21%) and or symptomatic treatment (24%). Our finding was similar to Luma *et al*. [29] where 68.2% patients needed the change in the regimen, and 31.8% were maintained on the same regimen with their ADRs subsided through symptomatic treatment. Abdissa *et al.* [28] showed that 10% of the patients required withhold of their therapy or change in treatment due to severe toxicity.

Causality assessment as per WHO-UMC scale showed that most of the ADR were probable 55.5% and 45.5% were possible. Kumari *et al.* [24] showed that 88% of ADRs were probable and 12% were possible while Anwikar *et al*. [30] found 96.4% ADRs to be possible and 3.50% probable. Kumar *et al*. [20] and Jain *et al*. [21] also found maximum ADRs to be possible. Rechallenge was not done in our cases because of associated risk and ethical reasons.

As per Modified Schumock and Thornton scale, most of the ADR were not preventable (84.5%), while 15.5% of ADRs were probably preventable. Similar observation was seen by Kumari *et al*. [24] where the majority of ADRs (83.33%) were not preventable, but Modayil *et al*. [31] found that 88% of ADRs were probably preventable which was contrary to our findings.

According to Modified Hartwig and Siegel severity assessment scale of ADRs, 84 (38%) were mild, 123 (56%) were moderate, and 13 (6%) were severe in nature. Similar type of results was found by Anwikar *et al*. [30]where 8.77%, 77%, and 14.02% ADRs were mild, moderate, and severe, respectively. These results are in contrast to Sadiq *et al*. [17] and Kumar *et al*. [20] where the majority of ADRs were mild followed by moderate and severe in nature.

Limitations of study

- Small sample size.
- Short duration of the study.

CONCLUSION

Antiretroviral although, the milestone for the treatment of HIV/AIDS has very high potential for developing ADRs which mainly affects the CNS, GIT, hematological, dermatological, and hepatorenal system. The TLE regimen prescribed as per the WHO and NACO guidelines cause mainly CNS ADRs, especially with efavirenz. These ADRs were mild to moderate in nature and subside spontaneously after 2–3 weeks without discontinuing the treatment. Maximum ADRs were managed by counseling and or symptomatically. Some drugs such as zidovudine and stavudine show ADRs such as anemia, neutropenia, and peripheral neuropathy after long-term treatment. Hence, active PV is needed for identification, prevention, and management of such ADRs developed by ART. This ensures not only the safety of the patients but also compliance to the treatment which is necessary for optimal therapeutic outcomes and to improve quality of life.

AUTHOR'S CONTRIBUTION

All the authors have contributed equally.

CONFLICTS OF INTEREST

The authors that they have none to declare.

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