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Research Article

A RETROSPECTIVE ANALYSIS OF SPONTANEOUSLY REPORTED ADVERSE DRUG REACTIONS TO ANTIRETROVIRAL THERAPY DURING AND POST-TRANSITIONAL PHASE OF DOLUTEGRAVIR

KATIKITALLA SWAROOPA[1], PILLA S SURYA DURGA DEVI[2]*, S KEERTHANA[1], R SRINIVASA RAO[1]

[1]Department of pharmacology, Rangaraya Medical College, Kakinada, Andhra Pradesh, India. [2]Adverse Drug Monitoring Center, Rangaraya Medical College, Kakinada, Andhra Pradesh, India.
*Corresponding author: Dr. Pilla S Surya Durga Devi; Email: sreesuryadurgadevi@gmail.com

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ABSTRACT

Objectives: The main objective of this study was to analyze the pattern of reported adverse drug reaction (ADRs) in people receiving antiretroviral therapy (ART) mainly during and post-transitional phase of dolutegravir-based regimens.

Methods: This is a retrospective observational study initiated after the approval of the Institutional Ethics Committee and from the ART Center. Sources of data are spontaneously reported ADR data of human immunodeficiency virus (HIV) persons to the ADR monitoring center (AMC).

Results: A total of 190 patients who are on ART reported at AMC from April 2020 to June 2022 had a total of 204 ADRs. Among them, 108 (57%) were females and had a higher prevalence than 82 (43%) males. ADRs were higher among the age group of 41–50 years (33.68%) followed by 31–40 years (32.10%). Among dolutegravir-based regimens, tenofovir, lamivudine, and dolutegravir were given to more patients (118). The most common ADRs encountered were peripheral neuropathy 16.66%, followed by hyperglycemia (14.21%), renal toxicity (10.29%), hyperbilirubinemia (9.31%), and anemia (7.84%) of all ADRs.

Conclusion: In this study, it has been observed that HIV patients on dolutegravir-based regimens are associated with more ADRs. Nervous system disorders were the most commonly observed group of ADRs, followed by metabolism and nutritional disorders, the others being skin diseases and renal toxicity. This incidence of ADRs to ART calls for efficient pharmacovigilance surveillance to improve patient care and drug safety.

Keywords: Dolutegravir, Antiretroviral regimen, Peripheral neuropathy, Hyperglycemia, Adverse drug reactions.

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INTRODUCTION

The human immunodeficiency virus (HIV) weakens a person's resistance to opportunistic infections such as tuberculosis, fungal infections, serious bacterial infections, and various malignancies by attacking the body's immune system, particularly the white blood cells known as CD4 cells. Antiretroviral therapy (ART) should be started as soon as feasible after an HIV diagnosis, and patients should frequently be checked using clinical and laboratory parameters. If ART is taken without fail, it also prevents HIV transmission to others [1]. The main goal of ART is to reduce the viral load in blood to undetectable traces (<50 copies/ml). Adherence to ART is important to maximize the clinical benefits on mortality and morbidity and to reduce the risk of drug resistance [1]. The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), which are commonly the "backbone" of the therapy, are the medication classes employed in this treatment; include zidovudine (Z), stavudine (S), lamivudine (L), tenofovir (T), and abacavir (A) and the non-NRTIs (NNRTIs) which include nevirapine (NVP) and efavirenz (E). Protease inhibitors include lopinavir (Lp), atazanavir (Atz), ritonavir (R), and nelfinavir. Integrase inhibitors include dolutegravir (D), raltegravir (R), and elvitegravir (E). There are several combinations of two NRTIs and one NNRTI available for treatment of HIV, including TLE, TLD, ALD, TLLpR, ZLLpR and ZLD [2]. Until now the first-line regimen for managing HIV is the TLE regimen. However, efavirenz usage has been limited due to adverse neurosensory effects and a low genetic barrier to resistance. Hence, it has been replaced by the dolutegravir (DTG)-based regimen since dolutegravir has a high genetic barrier to resistance [3].

Adverse drug reactions (ADRs) to ART in PLHIV are a major cause of non-compliance to medication, which leads to failure of therapy. These ADRs may be acute or chronic, mild or serious, and are quite common phenomena affecting both individual patients and public health. Monitoring and reporting of ADRs to ART centers in the Indian people are very significant [4]. To assess the ADRs profile of ART, numerous research has been carried out in Western and African populations; however, there are few similar studies in the Indian population [5]. ADRs associated with routinely prescribed antiretroviral medications (ART) were the focus of this study.

The main objective of this study was to analyze data of reported ADRs in people receiving ART mainly during and post-transitional phase of dolutegravir-based regimens and also to find out the pattern of the ADRs and to observe data for signals and find out the frequency of preventable ADRs to reduce the harm to the patients.

METHODS

A retrospective observational study was conducted after approval was obtained from the ART center and Institutional Ethics Committee. The sources of the data include the voluntarily reported ADR cases of HIV-infected individuals of any age or gender who took any ART medication as part of their ART between April 2020 and June 2022 to the ADR monitoring center (AMC) under the Pharmacovigilance Programme of India. The causality was assessed with the help of the World Health Organization (WHO)-UMC causality categories and the Naranjo ADR probability scale [6,7]. The extent of severity of all the cases was assessed by the Modified Hartwig and Seigel scale and this scale assists to assess the severity of the ADR as mild (level 1, 2), moderate (level 3, 4a, and 4b), and severe (level 5, 6, and 7) [8]. Drug withdrawal, dose reduction, additional treatment for ADR, and no change in a

regimen with any additional treatment are some of the management options available for the treating physicians. Modified Schumock and Thornton Criteria were used to assess preventability ADRs as definitely preventable, probably preventable, and not preventable [9]. Microsoft Excel 2016 was used to do a descriptive analysis on the data, and the results were presented as numbers and percentages.

RESULTS

A total of 190 reports were received from ART to AMC-RMC during the period from April 2020 to June 2022. Of 190 patients are on ART, 181 patients had a single reaction, 8 patients had 2 reactions, and 1 patient had 3 reactions. Among them, 108 (57%) were females and had a higher prevalence than males 82 (43%). ADRs were higher among the age group of 41–50 years (33.68%), followed by 31–40 years (32.10%). Details are shown in Table 1.

Among 190 patients, 118 patients received tenofovir, lamivudine, and dolutegravir (TLD) regimen; 21 patients received tenofovir, lamivudine, atazanavir, and ritonavir (TLAR); 16 patients received zidovudine, lamivudine, atazanavir, and ritonavir (ZLAR); 14 patients received tenofovir, lamivudine, and efavirenz (TLE) regimen; 6 patients received zidovudine, lamivudine, dolutegravir (ZLD), 4 patients received Abacavir, lamivudine, Dolutegravir (ALD) regimen, zidovudine, lamivudine, efavirenz (ZLE) and zidovudine, lamivudine, and nevirapine (ZLN) regimens, were received by 3 patients each. Dolutegravir+atazanavir+ritonavir (D+ATV+R) and tenofovir, lamivudine, lopinavir/ritonavir (TLLR) regimens were received by 2 patients each. Abacavir, lamivudine, lopinavir, ritonavir (AL+L/R), and dolutegravir, lopinavir, ritonavir D+ Lp/R regimens were received by 1 patient each (Table 2).

Among dolutegravir-based regimens, TLD was given to more patients (118). TLD contributes to about 118 ADRs, ZLD contributes to 6 ADRs, ALD contributes to 4 ADRs, DAtvR contributes to 2 ADRs and DLp/R contributes to 1 ADR. Dolutegravir -based regimens and no of ADRs are depicted in Fig. 1.

Nervous system disorders (29.92%) accounted for the maximum number of reported ADRs, followed by metabolism and nutritional disorders (17.15%), skin and subcutaneous diseases (14.70%), renal and urinary disorders (10.29%), and blood and lymphatic disorders (7.84%) (Table 3). The most common ADRs encountered were peripheral neuropathy 16.66%, followed by hyperglycemia (14.21%), renal toxicity (10.29%), hyperbilirubinemia (9.31%), and anemia (7.84%) of all ADRs. The contribution of ADRs by each regimen is shown in Table 4.

Causality assessment was done by the WHO and NARANJO scales. Out of 204 reactions, for 78% (158) of reactions, the dose is not changed and for 20% (41) of reactions, the drug has been withdrawn. Of the total of 204 ADRs, 18% (37) of reactions are given treatment, and 82% (167) of reactions are referred to tertiary care hospitals.

Severity assessment was carried out by a modified Hartwig and Siegel Scale, in which maximum ADRs were mild 158 (77.45%), followed by moderate 45 (22.05%) and severe 1 (0.49%). Regarding the seriousness of the reactions, only 2% are hospitalized and 92% are non-serious.

Preventability was assessed according to the Schumock and Thorton Scale; in our study, all cases were definitely preventable.

DISCUSSION

HIV patients have found ART to be beneficial, but it is also linked to a number of ADRs affecting numerous body systems.

Similar to Rukmangathen *et al.* and Patil *et al.*, females were found to have a greater incidence of ADRs (57%) than males (43%) in our study. An explanation for this gender difference in ADR incidence could be a gender-specific difference in, fat composition, body mass index, hormonal effects, drug susceptibility, or genetic constitutional differences on the levels of various enzymes although it has not been proven conclusively [4,10,11].

In the present study, the age group of 41–50 years had the highest prevalence of ADRs (33.68%), followed by that of 31–40 years (32.1%). These findings agree with those of other studies conducted by Lihite *et al.*, Rukmangathen *et al.*, and Patil *et al.* The majority of the study participants were between the ages of 31 and 50, which would explain this. Due to their higher levels of sexual activity and

Table 1: Baseline characteristics of patients who had experienced ADR with ART

Variable	n (%)
Sex	
Male	82 (43)
Female	108 (57)
Age distribution (years)	
<20	4 (2.1)
21–30	26 (13.68)
31–40	61 (32.1)
41–50	64 (33.68)
51–60	27 (14.21)
>60	8 (4.21)
Number of reactions	
Single	181 (95.26)
Double	8 (4.21)
Triple	1 (0.52)

ADRs: Adverse drug reactions, ART: Antiretroviral therapy

Table 2: Distribution of ART regimen in the study population

ART regimen	Number of patients
TLD	118
TLAR	20
ZLAR	16
TLE	14
ZLD	6
ALD	4
ZLE	3
ZLN	3
TLLR	2
D + ATV + R	2
D + LP/R	1
AL + L/R	1

ART: Antiretroviral therapy, TLAR: Tenofovir, lamivudine, atazanavir, ritonavir, ZLAR: Zidovudine, lamivudine, atazanavir, ritonavir, TLD: Tenofovir, lamivudine, and dolutegravir, TLE: Tenofovir, lamivudine, efavirenz, ZLD: Zidovudine, lamivudine, dolutegravir, ZLE: Zidovudine, lamivudine, efavirenz, ZLN: Zidovudine, lamivudine, and nevirapine, TLLR: Tenofovir, lamivudine, lopinavir/ritonavir, D + ATV + R: Dolutegravir + atazanavir+ ritonavir, AL+L/R: Abacavir, Lamivudine, Lopinavir, Ritonavir

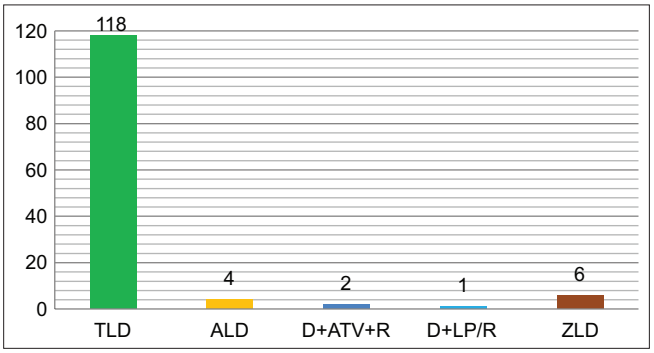

Fig. 1: Dolutegravir-based regimen induced adverse drug reactions

Table 3: System organ classification of ADRs

SOC (%)	Reaction term	n
Nervous system disorder (29.92)	Peripheral neuropathy	34
	Giddiness	14
	Headache	3
	Insomnia	5
Metabolism and nutritional disorder (17.15)	Hyperglycemia	29
	Hyperlipidemia	6
Renal and urinary disorders (10.29)	Renal toxicity	21
Hepatobiliary disorders (10.78)	Hyperbilirubinemia	19
	Jaundice	3
Blood and lymphatic system disorders (7.84)	Anemia	16
Skin and subcutaneous disorders (14.70)	Rash	13
	Itching	8
	Itchy rash	5
	Hyperpigmentation	2
	Melanonychia	1
	Steven Johnson syndrome of B/L eye	1
Gastrointestinal disorders (9.80)	Vomiting	10
	Nausea	6
	Abdominal distension	2
	Diarrhea	1
	Interstitial pancreatitis	1
General disorders and administration site condition (1.47)	Fever	1
	General weakness	1
	Body pains	1
Endocrine disorder (0.49)	Gynecomastia	1

SOC: System organ classification, ADRs: Adverse drug reactions

Table 4: ADR distribution by each regimen

Reaction	Regimen											
	TLD	ALD	D + Atv + R	D + Lp/R	AL + L/R	TLE	TLAR	TLLR	ZLD	ZLAR	ZLE	ZLN
Peripheral neuropathy	32	-	1	-	-	-	-	1	-	-	-	-
Hyperglycemia	27	1	-	-	-	-	-	-	1	-	-	-
Renal toxicity	19	-	-	-	-	1	1	-	-	-	-	-
Anemia	1	-	-	-	-	-	-	-	4	7	2	2
Hyperbilirubinemia	1	1	1	1	-	-	11	-	-	4	-	-
Giddiness	6	-	-	-	-	7	-	-	-	-	-	-
Vomiting	4	1	-	-	1	-	1	1	-	1	-	-
Hyperlipidemia	-	-	-	-	-	-	6	-	-	-	-	-
Itching	6	1	-	-	-	-	-	-	-	1	-	-
Fever	-	1	-	-	-	-	-	-	-	-	-	-
Nausea	1	-	-	-	-	3	-	-	-	1	-	-
Itchy rash	4	-	-	-	-	-	-	-	-	1	-	-
Abdominal distension	1	1	-	-	-	-	-	-	-	-	-	-
Hyperpigmentation	1	-	-	-	-	-	-	-	-	-	-	1
Rash	7	-	-	-	-	4	-	-	-	1	-	-
Headache	3	-	-	-	-	-	-	-	-	-	-	-
Jaundice	-	-	-	-	-	-	2	-	-	1	-	-
Insomnia	4	-	-	-	-	-	-	-	-	-	-	-
General weakness	1	-	-	-	-	-	-	-	-	-	-	-
Gynecomastia	-	-	-	-	-	-	1	-	-	-	-	-
Body pains	1	-	-	-	-	-	-	-	-	-	-	-
Diarrhea	1	-	-	-	-	-	-	-	-	-		-
Melanonychia	-	-	-	-	-	-	-	-	1	-	-	-
Interstitial Pancreatitis	-	-	-	-	-	1	-	-	-	-	-	-
SJS of B/L eyes	-	-	-	-	-	-	-	-	-	-	1	-

ADR: Adverse drug reactions

economic productivity, we may have found the bulk of ADRs in this age group [4,10,11].

In our study, a dolutegravir-based regimen is linked to 131 out of 204 ADRs. More ADRs (64.21%) on dolutegravir-based regimens are a result of the recent switch from efavirenz to dolutegravir. Out of which 118 (57.84%) of the ADRs were reported in patients who were on a TLD regimen as now it is considered an ideal first-line ART regimen for adults and adolescents.

Nervous system disorders (29.92%) accounted for the maximum number of reported ADRs, followed by metabolism and nutritional disorders (17.15%), skin and subcutaneous diseases (14.70%), renal and urinary disorders (10.29%), and blood and lymphatic disorders (7.84%).

The most common ADRs encountered were peripheral neuropathy 16.66%, followed by hyperglycemia (14.21%), renal toxicity (10.29%), hyperbilirubinemia (9.31%), and anemia (7.84%) of all ADRs. The

exact reason behind peripheral neuropathy is not known and there are no related studies yet. The diagnosis and subsequent treatment of drug-induced peripheral neuropathy depend on the physician's expertise and awareness of the problem [12]. These cases were given pyridoxine 50 mg once daily dose. DTG interferes with cellular insulin signaling, results in abnormalities in lipid metabolism, and produces obesity in patients. Obesity may then trigger the development of insulin resistance, which leads to elevated blood glucose levels [13]. It was proposed that the INSTI-induced hyperglycemia was caused by the chelation of magnesium, thereby inhibiting the release and signaling of insulin [14]. Uridine diphosphate glucuronosyltransferase (UGT), the enzyme in charge of bilirubin conjugation in the liver, is inhibited by Atazanavir. This causes hyperbilirubinemia. Based on their genetic similarities, the three UGT subfamilies UGT1A, UGT2A, and UGT2B have been found. UGT1A1, the principal enzyme of the UGT1A subfamily, is mostly expressed in the liver and gastrointestinal tract and is effective in the efficient elimination of bilirubin [15]. Tenofovir-induced renal toxicity is explained by depleting mitochondrial DNA, which results in mitochondrial toxicity, other reactions seen toward other NRTIs are less common with tenofovir [5]. Zidovudine is well known for suppressing bone marrow, which results in anemia and thrombocytopenia [5].

According to the Naranjo scale's assessment of causality, ADRs were probable, and according to the WHO scale, they were possible. There was no definite and unlikely ADR. To determine whether drug discontinuation is necessary and to prevent the future occurrence of ADRs, it is crucial to conduct a causality assessment using the WHO assessment scale or Naranjo's scale of the suspected drug reaction, as well as to educate patients to avoid the development of ADRs in the future [11,16].

Severity assessment was carried out by a modified Hartwig and Siegel Scale, in which maximum ADRs were mild 158 (77.45%), followed by moderate 45 (22.05%) and severe 1 (0.49%). Most of the cases were non-serious and 17 cases were serious cases which require hospital admission. Treatment was given for 37 cases and the remaining cases (166) were referred to tertiary care hospitals.

The drug has been withdrawn for 41 reactions most of which are renal toxicity and anemia. For 158 cases dose was not changed. Preventability was assessed according to Schumock and Thorton Scale; in our study, all cases were definitely preventable as there was a known treatment for these ADRs.

This study was a retrospective study so we are unable to perform a patient follow-up. Close follow-up of patients is needed during ART treatment to track and manage both early and late ADRs. Treatment given to manage ADR is also unknown because most of the cases were referred to tertiary care hospitals. There is a need for further studies on ADRs related to dolutegravir-based regimens as this is newly introduced so that we can identify unlabeled ADRs. Apart from anemia, we did not examine other laboratory markers of drug toxicity with the potential to affect virologic outcomes.

CONCLUSION

In this study, dolutegravir-based regimens are associated with more ADRs. Nervous system disorders were the most commonly observed group of ADRs, followed by metabolism and nutritional disorders, the others being skin diseases and renal toxicity. If taken appropriate measures such as drug withdrawal, dose adjustments, and/or immediate initiation of supportive treatment markedly reduces the harm or burden associated with the ADRs. Early detection, close monitoring, and voluntary reporting of ADRs help foresee and reduce the chance of ADRs and thus improve the quality of life of the patients.

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AUTHORS' CONTRIBUTION

The authors confirm their contribution to the paper as follows: Literature search, analysis and interpretation of results and draft manuscript preparation: Author-1, study conception, design, data collection, and manuscript editing: Author-2, literature search and manuscript preparation: Author-3, and Manuscript editing and manuscript review: Author-4. All authors reviewed the results and approved the final version of the manuscript.

CONFLICT OF INTERESTS

We declare that we have no conflicts of interest.

AUTHORS FUNDING

Nil.

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