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Evaluation of the Adverse Effects of Tenofovir-Lamivudine-Dolutegravir Combination Regimen in People Living with HIV in Sierra-Leone

Sikiru O Usman[1,2], Timothy F Kamara[2], AbdulWasiu A Busari, Ibrahim A Oreagba[1,2] and Esther O Agbaje[1,2]

[1]Department of Pharmacology, Therapeutics and Toxicology, Faculty of Basic Medical Science, College of Medicine of the University of Lagos, Lagos State, Nigeria

[2]Pharmacovigilance Department, African Centre of Excellence for Drugs Research, Herbal Medicine Development and Regulatory Service

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***Corresponding Author:**
Sikiru Olatunji Usman
Department of Pharmacology,
Therapeutics and Toxicology,
Faculty of Basic Medical Science,
College of Medicine,
University of Lagos, Lagos State,
Nigeria.
E-mail:
susman@unilag.edu.ng;
osusman1967@gmail.com.
Tel: +2347066263713.
[Orcid number:
0000-0001-7860-0442.
Google Scholar ID:
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ABSTRACT

Background: Dolutegravir-based antiretroviral regimen is one of the highly effective antiretroviral therapies that were introduced recently for the treatment of HIV in Sierra-Leone. However, its adverse effects have not been fully elucidated in patients living with HIV in Sierra-Leone.

Objectives: This study aimed to evaluate the adverse effects of tenofovir/lamivudine/dolutegravir (TDF/3TC/DTG) in patients living with HIV in Sierra-Leone.

Methods: This is a retrospective study involving the review of charts reporting adverse drug effects (ADEs) to TDF/3TC/DTG from five Hospitals in Freetown, between 1st July 2021 and 30th June 2024, for participants above 18 years. Patient's case files were used as main sources of data collection. These ADEs were analyzed using SPSS version 27 for the type of reactions, body systems involvement, and severity of the reaction, interventions used in the management of the ADEs and the risk factors for ADEs to TDF/3TC/DTG.

Results: The ADEs of TDF/3TC/DTG were reported in 132 of the participants giving a prevalence of 35.5 %. They were mild or moderate and were mostly anorexia (29; 7.9%), insomnia (25; 6.8%), vomiting (24; 6.5%), and pruritus (2, 0.5%).

Conclusion: Dolutegravir-based antiretroviral regimen of tenofovir-lamivudine-dolutegravir combination was well tolerated among adult patients living with HIV in Sierra-Leone. The adverse events reported were few and mild and occurred in less than half of the participants. However, futher studies are required to investigate the safety of the regimen in children and pregnant women.

INTRODUCTION

Infection with human immune-deficiency virus (HIV) remains a global concern with an estimated 40.8 million people living with HIV globally[1]. In 2024, an estimated 1.3 million people were newly infected and 630,000 died of HIV world-wide.[1,2] Sierra-Leone is a small country in West Africa with a population of 8.8 million people[3] and low HIV

prevalence of 1.7 %, making it about 77000 people living with HIV in this Country[4]. However, the vulnerability of individuals to HIV in Sierra-Leone is compounded by many risk factors, such as poverty, economic deprivation, and a history marred by a decade-long civil strife and an Ebola virus outbreak that claimed more than 4000 lives.[6]

Although antiretroviral therapy has been effective in alleviating the burden of HIV[7], the treatment is lifelong and associated with adverse effects[8] which makes it difficult for patient to adhere adequately. Consequently, this can lead to therapeutic failure, treatment discontinuation and switch to another regimen.[9] Hence there is a need for continuous search for an alternative therapy and development of new antiretroviral drugs with high efficacy and minimal ADEs

Dolutegravir (DTG), a second-generation integrase strand transfer inhibitor was approved in combination with lamivudine and tenofovir for the treatment of HIV in August 2013 by the U.S. Food and Drug Administration (FDA)[10] and later in January 2014 by the European Medicines Agency (EMA). These approvals marked the beginning of DTG's global use as a highly effective integrase strand transfer inhibitor (INSTI) for HIV treatment.

The World Health Organization (WHO) recommended dolutegravir-based antiretroviral therapy regimen as a preferred first- and second-line treatment for adults and children with HIV-1 infection in 2018.[11] The WHO also recommended DTG-based ART as the preferred first-line and second-line treatment for all populations, including pregnant women and those of childbearing potential in 2019.[12] Following the WHO recommendation, dolutegravir-based ART was adopted by Sierra-Leone in 2020 for the treatment of HIV[13] and has since proven to be very effective.[14] However, there is paucity of data about its ADEs in patients living with HIV in Sierra-Leone. Hence this study aimed to evaluate the ADEs of TDF/3TC/DTG in patients living with HIV in Sierra-Leone and to report their prevalence, risk factors and how they were managed.

METHODS

Study Site

The study was carried out at the HIV/AIDS Outpatient Clinics of Five Hospitals located in Freetown, Sierra Leone; namely University of Sierra Leone Teaching Hospital Complex, Connaught Hospital (USLTHCCH), 34 Military Hospital (34 MH), Lumley Government Hospital (LGH), Kingharman Road Maternity and Child Health Hospital (KRMCHH) and Rokurpa Maternity and Child Health Hospital (RMCHH).

Study Design

This is a retrospective cohort study. Data of 372 participants living with HIV who were prescribed TDF/3TC/DTG between 2021 and 2024, in the HIV clinic of five different hospitals in Freetown, were extracted from their electronic medical records which were regularly updated. The data of all the participants who were being treated with TDF/3TC/DTG were initially extracted into an excel sheet and the 372 participants who met the inclusion criteria were randomly selected. The data extracted from their medical record included demographics of the patients, adverse events experienced and the drugs used in the management of the adverse effects. The data were subjected to statistical analysis to obtain the required information.

Sample Size Determination

A sample involving 372 patients living with HIV and being treated with TDF/3TC/DTG was used for the study. The sample size was determined based on a standard formula.[15] The participants were drawn from 5 hospitals in Freetown as stated above

Inclusion and exclusion criteria

Male and female patients who were ≥18 years, living with HIV and attending the HIV/AIDS outpatient clinics at the study centres between 2021 and 2024, and taking TDF/3TC/DTG were included in the study. while Pregnant women and those breastfeeding who were living with HIV, patients living with HIV and also having comorbidities such as hypertension, diabetes mellitus, tuberculosis ~~and~~ renal impairments, patients on ART other than TDF/3TC/DTG were excluded from the study.

Ethical Considerations

The study was approved by the Research Ethics Committee of Sierra-Leone. Approval was also obtained from the Directors of the hospitals used for the study. Confidentiality of the data extracted was maintained.

Data Analysis

The data collected were analyzed using IBM SPSS version 27. The variables were recorded in frequencies and percentages using descriptive statistics. Risk factors for adverse drug effects of TDF/3TC/DTG were determined using chi square test. Data were considered significant at 95% confidence level and p-value of 0.05

RESULTS

Sociodemographic data of the participants

Data for 372 patients were extracted and analyzed in this study. The patient distribution according to the hospitals is USLTHCCH (76; 20.4%), 34 MH (64;

17.2%), LGH (76; 20.4%), KRMCHH (40; 10.8%), and RMCHH (85; 22.8%). The patients were predominantly female (239; 65.2%) and mostly in the age group 21 to 30 years (151; 40.6%). Only 144 (38.7%) patients were married and nearly two-third had secondary or tertiary education (Table 1).

Table .1: Sociodemographic data of participants

Parameters	**Group**	**n (%)**
Participants	Total	372 (100.0)
Gender	Male	133 (35.8)
	Female	239 (65.2)
Age (Years)	Median (IQR)	32 (27-41)
	18 - 20	10 (2.7)
	21 – 30	151 (40.6)
	31 – 40	118 (31.7)
	41 – 50	60 (16.1)
	51 - 60	27 (7.3)
	> 60	6 (1.6)
Marital Status	Single	195 (52.4)
	Married	144 (38.7)
	Divorced	8 (2.2)
	Widow/widower	25 (6.7)
Educational Qualification	Illiterate	15 (4.0)
	Primary	41 (11.0)
	Secondary	184 (49.5)
	Tertiary	132 (35.5)
Tribe	Creole	25 (6.8)
	Fullah	30 (8.1)
	Kissy	2 (0.5)
	Kono	14 (3.8)
	Kuranko	5 (1.3)
	Limba	55 (14.8)
	Loko	24 (6.5)
	Mandigo	20 (5.3)
	Mende	67 (18.0)
	Shebero	6 (1.6)
	Susu	9 (2.4)
	Temme	115 (30.9)

*n: number of participants; %: percentage of participants; GH: Government Hospital.

Documentation and Classification of Adverse Drug Effects to TDF/3TC/DTG

The prevalence of ADEs to TDF/3TC/DTG was 132 (35.5%) [with the most frequent one being anorexia 29 (7.9%), followed by insomnia 25 (6.8%) and vomiting 24 (6.5%), while itching of the skin accounted for the least ADEs reported 2 (0.5%). The ADEs to TDF/3TC/DTG were predominantly mild 125 (38.6%). However, few of them were moderate, 43 (11.6%). It is noteworthy that none of the patients experienced all the adverse events listed while some of them experienced more than one ADEs The CNS (89; 24%) is the part of the body that is mostly affected with the adverse events followed by the gastrointestinal tract (77; 20.9%) while the effects on the cardiovascular system (2; 0.5%) was the least (Table 2).

Table 2: Organ-system classification and types of the adverse effects of TDF/3TC/DTG

Organ-system affected and the type of adverse effects of TDF/3TC/DTG	n (%)
Musculoskeletal system	
Facial swelling	3 (0.8)
Swollen feet	6 (1.6)
Renal system	
Elevated creatinine level	5 (1.3)
Uraemia	5 (1.3)
Cardiovascular system	
~~High~~ Elevated Blood Pressure	2 (0.6)
CNS	
Dizziness	5 (1.3)
Fatigue	7 (1.9)
Headache	23 (6.2)
Insomnia	25 (6.8)
Anorexia	29 (7.8)
Dermatological system	
Pruritus ~~Itching skin~~	2 (0.5)
Gastrointestinal System	
Nausea	17 (4.6)
Diarrhea	18 (4.9)
Abdominal pain	18 (4.9)
Vomiting	24 (6.5)

*n: number of participants; %: percentage of participants; GH: Government Hospital.
TDF: tenofovir, 3TC: lamivudine, DTG: dolutegravir

Drug used to Manage Adverse Drug Events to TDF/3TC/DTG

The co-prescribed drugs for the treatment of adverse drug effects to TDF/3TC/DTG are presented in Table 3. Among Sierra-Leoneans with HIV, oral rehydration salt 31 (8.3%) was the most frequently prescribed non-ART drug which was recommended to individuals who developed diarrhea following the use of TDF/3TC/DTG. While the least prescribed drug was cetirizine which was recommended for the treatment of itching associated with the use of TDF/3TC/DTG.

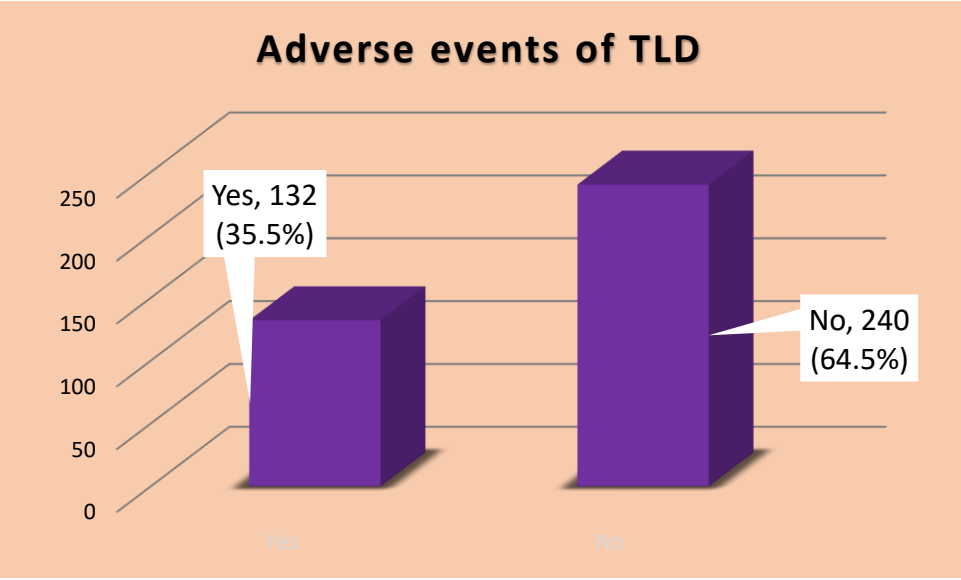

Figure 1: Prevalence of adverse effects to TDF/3TC/DTG
*Number of Participants, %: Percentage of Participants

Table 3: Drug used to Manage Adverse Drug Events to TDF/3TC/DTG

Drug prescribed to manage ADEs to TDF/3TC/DTG	Uses	n (%)
Paracetamol	Headache	17 (4.6)
Paracetamol+codeine	Headache/ body pain	14 (3.8)
Metoclopramide	Nausea and vomiting	19 (5.1)
Amlodipine	High blood pressure	2 (0.6)
Frusemide	Swollen leg	4 (1.1)
Multivitamins	Anorexia	28 (7.5)
Haematinics	fatigue	26 (7.0)
Oral rehydration salt	Vomiting/ diarrhea	31 (8.3)
Hyoscine butylbromide	Abdominal pain	11 (3.0)
Metronidazole	Diarrhea	12 (3.2)
Cetirizine	Body itching	2 (0.5)

n: number of participants, %: percentage of participants, TDF: tenofovir, 3TC: lamivudine, DTG: dolutegravir

The Prevalence and Reasons for Discontinuation of TDF/3TC/DTG

Only few 7 (1.9 %) of the participants were discontinued on TDF/3TC/DTG as a result of kidney toxicity indicated by the high creatinine and urea levels. All the seven patients were placed on abacavir/lamivudine/dolutegravir (ABC/3TC+DTG). None of the patients was discontinued due to treatment failure of TDF/3TC/DTG (Figure 2).

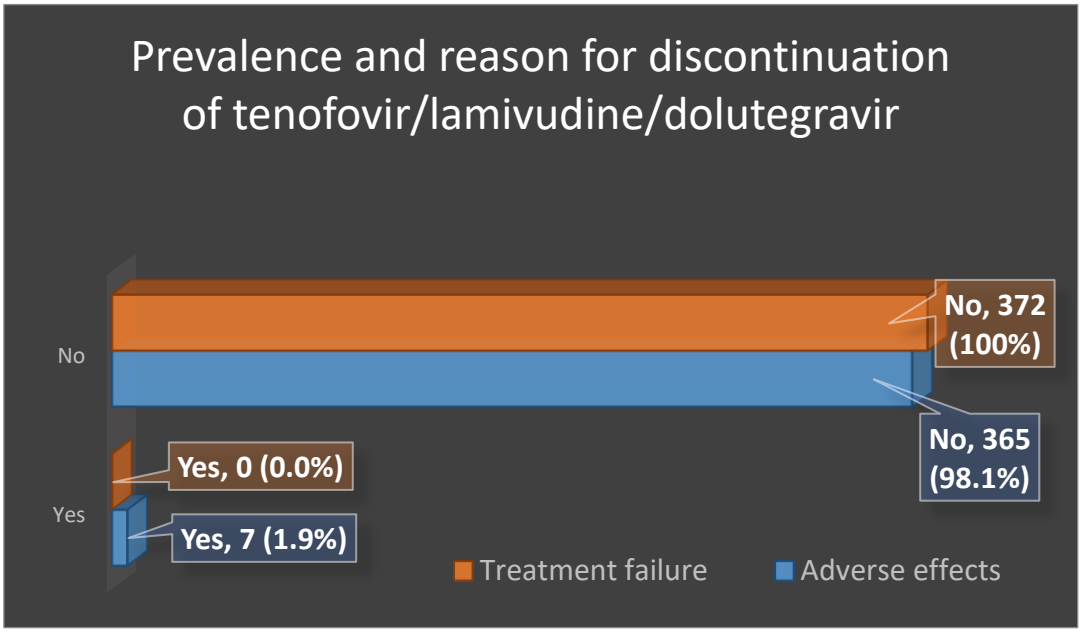

Figure 2: The prevalence and reasons for discontinuation of TDF/3TC/DTG

Risk Factors Associated with Adverse Drug Events to TDF/3TC/DTG

According to this study, marital status and age were risk factors ($p<0.05$) for development of ADEs to TDF/3TC/DTG while gender and educational level were not ($p>0.05$). Married patients 63 (43.8%) and patients above 60 years of age [6 (100%)] were at high risk of experiencing ADEs to TDF/3TC/DTG.

Table 4: Risk Factors Associated with Adverse Drug Effects to TDF/3TC/DTG

Variables	Group	ADEs OF TDF/3TC/DTG n (%)		Odd ratio	p value
		Yes	No		
Gender	Male	51 (38.3)	82 (61.7)	1.21 (0.78-1.88)	0.227
	Female	81 (33.9)	158 (66.1)		
	Illiterate	7 (46.7)	8 (53.3)		0.081
Educational level	Primary	10 (24.4)	31 (75.6)		
	Secondary	59 (32.1)	125 (67.9)		
	Tertiary	56 (42.4)	76 (57.6)		
	Single	45 (23.1)	150 (76.9)		0.000
Marital status	Married	63 (43.8)	81 (56.2)		
	Divorced	2 (25.0)	6 (75.0)		
	Widow/Widower	22 (83.3)	3 (16.7)		
Age (yrs)	18-20	0 (0.0)	10 (100.0)		0.000
	21-30	21 (13.9)	130 (86.1)		
	31-40	38 (32.2)	80 (67.8)		
	41-50	41 (68.3)	19 (31.7)		
	51-60	1 (3.7)	26 (96.3)		
	> 60	6 (100.0)	0 (0.0)		

n: number of participants, %: percentage of participants, TDF/3TC/DTG: tenofovir/lamivudine/dolutegravir, ADEs: adverse drug effects

DISCUSSION

This study reported a predominant age group of 21-30 years among the participants in conformation to the report of previous studies.[7,16] This might be due to the fact that human are mostly sexually active within the age group. The demographic data in this study also confirm the fact that female gender are more infected with HIV than their male counterpart as previously reported.[17,18,19]

A prevalence (35.5 %) of ADEs to TDF/3TC/DTG was observed indicating that about a third of the participants had a minimum of one ADE to TDF/3TC/DTG while two-third of them did not. This finding is in conformity to report of previous studies[20-21] and may indicate relative safety of the dolutegravir-based ART regimen among people living with HIV in Sierra-Leone.

A total of fifteen different adverse drug events to TDF/3TC/DTG were documented of which the most common one was anorexia (29, 7.8%), followed by insomnia (25, 6.8%), vomiting (24, 6.5%) and headache (23, 6.2%). The least were itching (2, 0.5%), high blood pressure (2, 0.5%), swollen face (3, 0.8%), uraemia (5, 1.5%), elevated creatinine level (5, 1.5%), dizziness (5, 1.5%), swollen feet (6, 1.6%) and fatigue (7, 1.9%). To our knowledge, anorexia has not been previously reported as an adverse event nor effect of TDF/3TC/DTG, hence this may be a novel information on the safety profile of dolutegravir and being the most documented adverse event of TDF/3TC/DTG, it may be related to the genetic disposition of the people of Sierra-Leone. Conversely, insomnia and headache are CNS-related adverse effects which have been previously reported in many studies[23-25]. Although, fatigue was among the least reported adverse events, it may be an actual adverse effects of TDF/3TC/DTG, having been reported in many previous studies.[26-28] High penetration and concentration of dolutegravir in the brain may be responsible for its fatigue and other CNS adverse events.[27] And reduction in the dose of dolutegravir has been associated with resolution of the neuropsychiatric effects.[27] Itching, which was minimally reported, also has precursory reports.[21, 29-31] However, itching may also be caused by lamivudine[32, 33] which is one of the antiretroviral drugs in the dolutegravir-based regimen. Vomiting (24, 6.5%) was the third frequently reported adverse event in this study. It included one of the gastrointestinal adverse events which had been previously reported[33,34] even though it was not specifically singled out in these studies. However, it was well tolerated and did not lead to discontinuation of TDF/3TC/DTG. Facial swelling (3, 0.8%), though, less frequently reported, had been associated with development of immune reconstitution inflammatory disease in a patient on TDF/3TC/DTG, as previously reported.[36] Few Patients (7) discontinued TDF/3TC/DTG due to Kidney toxicity and were placed on ABC/3TC+DTG which was in line with WHO Treatment Guidelines, because ABC/3TC is safe in kidney disease, while Tenofovir Disoproxil Fumarate has been implicated in renal malfunction [37]. Hence the renal toxicity observed in the study is related to the tenofovir disoproxil fumarate (TDF)

component of the regimen rather than lamivudine nor dolutegravir as reported by many other studies[38-39] While marital status, found in this study as a risk factor for development of adverse effects to TDF/3TC/DTG, has not been previously reported, to our knowledge, the reverse is the case for age which has been reported by other study.[40]

CONCLUSION

Dolutegravir-based antiretroviral regimen of tenofovir-lamivudine-dolutegravir combination was well tolerated among majority of the adult patients living with HIV in Sierra-Leone. Only few adverse events which were predominantly mild and mainly included anorexia, insomnia and vomiting were observed. These adverse events occured in less than half of the patients and were significantly associated with age and marital status. Oral rehydration salt and multivitamins are commonly used drugs for the management of the adverse effects of TDF/3TC/DTG. However, further studies are required in a larger population for broader elucidation and investigation in vulnerable groups including the children and pregnant women.

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