Original Article

An Analysis of Pharmacovigilance Case Reports of Adverse Drug Events Attributable to Dolutegravir-based Antiretroviral Treatment for HIV in Zambia

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ABSTRACT

Background: In 2018, Dolutegravir (DTG)-based combination treatment was introduced in Zambia as the preferred first-line treatment for HIV infection in adults and adolescents weighing 35kg and above, with the exception of pregnant women. There is currently insufficient information regarding the safety of DTG-based combination regimen, including the types and frequency of suspected adverse drug events (ADEs) experienced and reported in Zambia. **Aim:** To describe ADEs experienced and reported among patients taking DTG-based regimen for HIV treatment in Zambia between the periods January 2018 to April 2019.

Methods: A descriptive cross-sectional design was used to review all spontaneous reports submitted by health workers and patients to the Zambia Medicines Regulatory Authority (ZAMRA) pertaining to suspected ADEs experienced by patients on DTG-based antiretroviral regimen during the period starting January 2018 to April 2019. Case reports were accessed from the national pharmacovigilance database at ZAMRA. Variables of interest were types and prevalence of suspected ADEs experienced and reported, onset and seriousness of the ADE.

Results: Forty-five spontaneous ADR reports received by ZAMRA between January 2018 and April 2019 involved 27 (62.8%) male and 16 (37.2%) female HIV patients. The mean age was 50 ± 11 years. Sixty ADE incidents were reported during the review period involving patients initiated on DTG-based regimen. The most reported ADEs were headache (n = 14), dizziness (n = 7), limb numbness (n = 5), insomnia (n = 5), and drowsiness (n = 5). Neurological and neuropsychiatric symptoms accounted for 30% (n = 18), followed by an altered sense of balance 16.7% (n = 10) of the suspected ADEs reported. No mortality was recorded but 17 (37.8%) cases experienced morbidity and 8 (17.8%) cases had therapy discontinued or changed secondary to ADEs.

Conclusion: Suspected neurological and neuropsychiatric ADEs were commonly experienced by the majority of patients on DTG-based antiretroviral regimen in Zambia. The low rate of ADE reporting among patients and healthcare providers remains a cause for concern. This must be addressed to improve medication safety monitoring.

INTRODUCTION

Current global recommendations advise the initiation of HIV treatment in all newly diagnosed patients with the use of integrase inhibitor-based antiretroviral regimens such as dolutegravir (DTG) which has shown to slow the rate of disease progression and immune suppression[1,2]. DTG is a second-generation integrase strand transfer inhibitor (INSTI) that acts by blocking the strand transfer step of retroviral DNA integration in the host cell thereby inhibiting HIV replication[3,4]. The World Health

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Organisation (WHO) recommends the use of a new fixed-dose combination of dolutegravir 50mg, tenofovir 300mg and lamivudine 300mg as the preferred first-line treatment of HIV infection in treatment naïve patients irrespective of CD4+ count[2]. As at end of 2017, almost 60 low-middle income countries (LMICs) adopted DTG-based combination antiretroviral regimens into their national treatment guidelines, largely based on evidence from studies done in high-income countries (HICs) that demonstrated efficacy, limited drug-drug interactions, and tolerability of DTG-based regimens[5].

DTG has been recommended to replace the standard dose efavirenz 600mg-based regimen previously used. A growing body of clinical evidence demonstrated that efavirenz (EFV) given at a standard dose of 600mg had important limitations in terms of adverse effects with over 50% of patients initiated on it experiencing short to long term neuropsychiatric effects such as dizziness, drowsiness, insomnia, confusion, loss of memory, agitation, hallucination, delusions, depression, abnormal dreams and impaired concentration lasting few weeks or months. Some of the long term adverse effects include suicidality, aggression, paranoia, anxiety, mania, neurocognitive impairment, and metabolic toxicities (dyslipidemia, dysglycemia and lipoatrophy)[6]. It also has safety concerns in the first trimester of pregnancy[7]. More effective and safer drugs could yield meaningful cost savings for health systems and improve quality of life for HIV patients[8].

Clinical trial data showed that DTG was a very well tolerated drug, with a lower overall incidence of adverse effects (<5%) when compared with EFV. The frequently reported adverse effects of DTG were gastrointestinal symptoms (nausea, vomiting), hypersensitivity skin reactions and central nervous system effects (insomnia, dizziness) which were often mild and self-limiting[9]. DTG discontinuation rates observed in clinical trials and in programme data were lower compared to EFV. European cohort studies detected an increased occurrence of neuropsychiatric side effects to DTG, including discontinuation rates in women and people over 60 years of age[10]. Despite the global shift in treatment guidelines, there still exists paucity of data concerning the safety of DTG in post-market surveillance of African populations using the drug. Consequently, there exist uncertainties about the potential adverse events, overlapping toxicities, drug interactions, and other population-specific safety concerns associated with DTG-based antiretroviral therapy. With the introduction of newer drugs for mass-scale administration comes an increased need for robust surveillance and reporting of safety information. As guided by Morimoto and colleagues, investigating the incidence, type, and preventability of ADEs and medication errors is crucial to improving the quality of health care delivery[11]. By definition, an ADE is an injury resulting from a medical intervention using a drug or a medication[12]. ADEs, potential ADEs, and medication errors can be collected by extraction from practice data, solicitation of incidents from health professionals, and patient surveys. Practice data include patient records, laboratory, prescription data, and administrative databases, and can be reviewed manually or screened by computer systems to identify signals[11].

Zambia is among countries in Sub-Saharan Africa with one of the highest HIV prevalence at 11.5% and 48, 000 new infections[13]. In the last decade, the country had about a million people living with HIV and successfully scaling up of combination antiretroviral therapy (ART) provision to over 900 000 clients[14]. At the end of 2017, 75% of people in need of antiretroviral treatment were receiving it[13]. Antiretroviral therapy for HIV is provided free of charge to every patient in Zambia's public healthcare sector and is a national health priority towards achieving the 90-90-90 goals established for member states by the Joint United Nations Programme on HIV/AIDS (UNAIDS)[15]. In June 2018, the government of Zambia rolled-out the Tenofovir alafenamide + Lamivudine or

Emtricitabine + Dolutegravir (TAF + XTC + DTG) combination regimen as the first-line treatment for all new HIV infection cases in adult patients, with exception of pregnant women[16,17]. Transition to DTG-based regimen was encouraged for patients who were on Tenofovir + Lamivudine + Efavirenz regimen and were virologically suppressed[17]. On the Zambian market, DTG comes in a fixed-dose tablet combination with Tenofovir and Lamivudine (TLD) and as a single-dose formulation containing DTG 50mg tablets. Following the introduction of DTG as a new drug in the combination ART regimen in Zambia, targeted spontaneous reporting of ADEs and other safety concerns was set up in 2018 by ZAMRA as part of it post-marketing surveillance role. Medicine safety information is continually required to inform national policy on their safe and rational utilisation. This paper described the ADEs experienced and reported among patients taking DTG-based treatment for HIV in Zambia from January 2018 to April 2019.

METHODS

Study design

A descriptive cross-sectional study was conducted.

Sampling

Only spontaneous reports related to DTG-based regimen that were reported by healthcare providers and patients from January 2018 to April 2019 and were recorded in the official database kept at the National Pharmacovigilance Unit (NPVU) at ZAMRA were considered. All the case reports (n = 45) submitted to NPVU during the period under review were included in the analysis.

Data collection

A dataset of individual case reports was accessed from the NPVU database. The spontaneous reports were routinely reported to ZAMRA using the official Adverse Drug Reaction (ADR) reporting forms and platforms. The form collects data on patient characteristics (e.g. age, sex, weight, etc.), description of the ADR/ADE or medicine-related problem, the current medications taken, the onset of ADR/ADE and its outcome. The dataset was exported into Microsoft Excel for purposes of data cleaning and collation.

Data analysis

Descriptive statistics were used to analyse primary variables of interest which included: demographic characteristics of patients, type and prevalence of suspected ADE experienced and its reported onset, seriousness, and outcome. Frequencies and proportions were used to describe the data. Fisher's exact test was used to measure associations between ADE and demographic variables. For statistical significance, a p-value less than 0.05 was accepted. All statistical analysis was done using Stata 13 software.

Ethical considerations

Data were all strictly anonymised and no names of patients or their personal details were used at any time. All data were confidentially managed by authors. Formal permission was obtained from the management of ZAMRA to access and utilise the secondary data from the institutional database, including publication of findings. This work was operational in nature.

RESULTS

Demographic characteristics of patients

Among the 45 ADR case reports reviewed, 62.8% involved male patients and 56.8% of the patients were aged above 50 years (Table 1).

Table 1: Patient demographics

Characteristic		Proportion, n (%)	p-value
Sex	Male	27 (62.8%)	0.0343*
	Female	16 (37.2%)	
Age (mean ± SD, range)		50 ± 11 (26– 86)	
Age category	≤50 years	19 (43.2%)	0.2864
	>50	25 (56.8%)	
HIV treatment status	Experienced	7 (15.6%)	-
	Naïve	2 (4.4%)	
	Not reported	36 (80.0%)	
Treatment indication	HIV	44 (97.7%)	0.0001*
	PEP	1 (2.2%)	

**Fisher's exact test statistically significant*

Adverse drug events experienced by patients on dolutegravir-based treatment

From the case reports reviewed, table 2 shows the ADE experienced by patients initiated on DTG-based regimen.

Table 2: Reported ADE incidents experienced by patients on DTG-based regimen

ADE Experienced and Reported	Frequency (n)	ADE Experienced and Reported	Frequency (n)
Headache	14	Nightmares	1
Dizziness	7	Angioedema	1
Limb numbness	5	Difficulty breathing	1
Insomnia	5	Rash	1
Drowsiness	5	Depression	1
Joint pain	4	Alopecia	1
Loss of appetite	4	Palpitations	1
Weakness	4	Bloating	1
Diarrhoea	4	Abdominal pain	1
Nausea and vomiting	4	Neck stiffness	1
Burning sensation in limbs	3	Hiccup	1
Malaise	3	Seizures	1
Pruritus	2	Sexual dysfunction	1
Constipation	2		
Blurred vision	1		

Table 3: Categories of suspected ADEs reported to be experienced by patients on DTG-based regimen

ADE category	Proportion (n, %)
Neurological & Neuropsychiatric	18 (30.0%)
Altered sense of balance (dizziness, drowsiness)	10 (16.7%)
General (malaise, fatigue, nausea)	10 (16.7%)
Gastrointestinal effects	8 (13.3%)
Neuropathy	7 (11.7%)
Hypersensitivity	3 (5.0%)
Musculoskeletal	2 (3.3%)
Cardiovascular effects	1 (1.7%)
Sexual dysfunction	1 (1.7%)
TOTAL	**60 (100%)**

Neurological and neuropsychiatric effects were frequently experienced among 30% (n = 18) patients initiated on DTG-based treatment. Dizziness, drowsiness, malaise, fatigue and nausea collectively accounted for 33.4% (n = 20) incidents reported (Table 3). Age of the patient and sex were statistically significantly associated with ADEs. When sex and age were considered (Figure 1 and 2), males and patients above 50 years of age experienced ADEs more frequently (Table 4). Neurological symptoms were largely experienced by patients aged above 50 years old (Figure 2).

Table 4: Distribution of ADE category by sex and age of the patient

ADE category	Sex (n, %)				Age in years (n, %)			
	Male	Female	Missing	*p-value**	5≤0	>50	Missing	*p-value**
Altered sense of balance (dizziness, drowsiness)	7 (18.9%)	3 (14.3%)	0	*0.7190*	4 (17.4%)	6 (17.1%)	0	*1.0000*
General (malaise, fatigue, nausea)	6 (16.2%)	2 (9.5%)	2 (100%)	*0.6882*	5 (21.7%)	4 (11.4%)	1 (50%)	*0.4674*
Neuropsychiatric	7 (18.9%)	2 (9.5%)	0	*0.4455*	6 (26.1%)	3 (8.6%)	0	*0.1440*
Neurological (headache)	5 (13.5%)	4 (19.0%)	0	*0.7060*	0	9 (25.7%)	0	*0.0057**
Gastrointestinal	6 (16.2%)	2 (9.5%)	0	*0.6882*	2 (8.7%)	6 (17.1%)	0	*0.4329*
Neuropathy	2 (5.4%)	4 (19.0%)	0	*0.1740*	2 (8.7%)	3 (8.6%)	1 (50%)	*1.0000*
Hypersensitivity	0	3 (14.3%)	0	*0.0454**	1 (4.3%)	2 (5.7%)	0	*1.0000*
Musculoskeletal	2 (5.4%)	1 (4.8%)	0	*1.0000*	2 (8.7%)	1 (2.9%)	0	*0.5696*
Cardiovascular	1 (2.7%)	0	0	*1.0000*	0	1 (2.9%)	0	*1.0000*
Sexual dysfunction	1 (2.7%)	0	0	*1.0000*	1 (4.3%)	0	0	*0.4318*
TOTAL	**37 (61.7%)**	**21 (35.0%)**	**2 (3.3%)**	**0.0059***	**23 (38.3%)**	**35 (58.3%)**	**2 (3.3%)**	**0.0440***

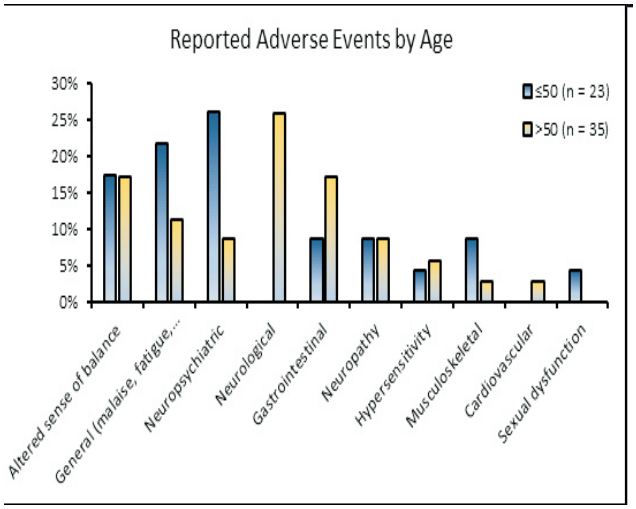

Figure 1: Distribution of reported ADE by sex of the patient

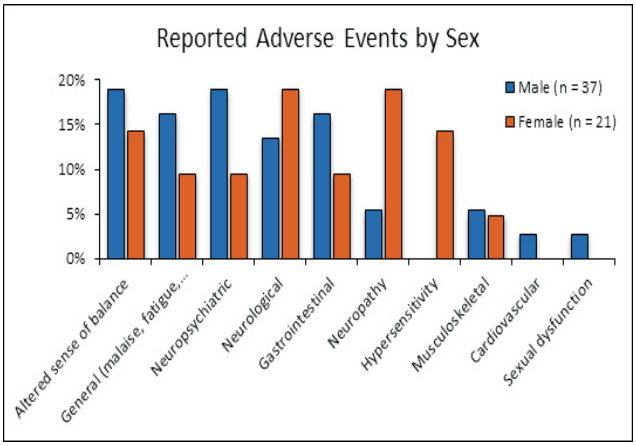

Figure 2: Distribution of reported ADE by age of the patient

The onset of ADEs

Only 23 out of 45 reports submitted had the onset of ADE indicated. The majority of incidents occurred less than 48 hours after initiation of TLD. Some ADEs (20.1%, n = 6) were reported to have commenced 1 to 7 days after commencement of the regimen (Table 5). It was a cause of concern that nearly half of the case reports (48.9%, n = 22) submitted did not indicate or had data on the onset of symptoms missing.

Table 5: Reported onset of ADE from the date of commencing DTG-based regimen

Onset of ADE from date of commencing DTG-based regimen	Frequency (n, %)	Missing/Not reported (n, %)
<24 hours	14 (60.9%)	22 (48.9%)
1 to 7 days	6 (20.1%)	
7 to 14 days	2 (8.7%)	
>14 days	1 (4.3%)	
TOTAL	**23 (51.1%)**	**22 (48.9%)**

Outcomes of ADEs reported

There was no case of mortality recorded at the time of reporting. Whereas a substantial number of patients (37.8%, n = 17) experienced morbidity and were hospitalised for treatment of the ADE (Table 6), a good number of them (31.1%, n = 14) recovered from the ADE. Similarly, due to the ADE experienced, only 17.8% (n = 8) had their DTG-based antiretroviral regimen discontinued or changed.

Table 6: Reported outcome of ADE

Outcome after ADE *(N = 45)*	Frequency (n, %)
Recovered	14 (31.1%)
Morbidity (Not recovered)	17 (37.8%)
Mortality	0 (0.0%)
Regimen discontinued or changed	8 (17.8%)
Not reported/Data missing	6 (13.3%)

DISCUSSION

This review utilised case reports related to DTG-based regimen submitted to ZAMRA from January 2018 to April 2019 through its targeted spontaneous reporting system. A total of 60 types of ADEs, each with varying frequency were extracted from the 45

case reports reviewed. Headache, altered sense of balance (dizziness, drowsiness), neuropsychiatric, and general effects such as malaise, nausea and fatigue were the most frequently reported ADEs (Table 3). Our finding agrees with Menard and colleagues who also found that neuropsychiatric symptoms such as sleep disturbances and irritability were frequently observed ADEs in a cohort of 2260 HIV patients in France[18]. In their study, 55 (10.6%) of the observed ADEs, with 28 (51%) of these being neuropsychiatric, led to discontinuation of DTG-based antiretroviral treatment. Borghetti and colleagues[19] as well as Bonfanti and colleagues[20] also reported similar findings of neuropsychiatric ADEs with DTG-based regimens. These ADEs were attributable to DTG. Notwithstanding, other scholars argued that neuropsychiatric adverse effects in patients treated with integrase strand transfer inhibitors (INSTIs) such as DTG and raltegravir is not an emergent story and appears to be a class effect[20,21].

Regarding the onset of the suspected ADEs, among the reports that indicated the onset date (n = 23), the majority (60.9%, n = 14) of AE's experienced were acute, occurring within 24 hours of commencing the DTG-based therapy while a few occurred 1 to 7 days after initiation of the regimen (Table 5). Other studies reported that symptoms of ADEs in patients on DTG-based regimens occurred within one month (median) after initiation of DTG[18]. The majority of reports (61.7%, n = 37) reviewed in this study did not indicate the onset date. This was perhaps due to incomplete reporting.

That there was no ADE-associated mortality reported among the cases that experienced ADEs was comforting. However, morbidity cases requiring hospitalisation were substantial (Table 6) with a number of cases (17.5%, n = 8) requiring discontinuation of treatment. This proportion was relatively high in spite of the relatively small sample in our study than that reported by Menard and colleagues in France who found that only 10.6% of DTG-associated ADEs led to discontinuation of therapy[18]. Our data did not, however, indicate the clinical or pharmacological reasons for discontinuation of the DTG-based regimen. Hoffmann and colleagues also found that the rates of discontinuation of DTG because of neuropsychiatric adverse events was significantly higher than for other INSTIs[10]. We found that ADEs were generally experienced more by older patients (>50 years old) ($p = 0.0440$). This finding was similar to other studies that showed that older patients (aged more than 60 years were significantly associated with ADE occurrence[10,18]. Whereas other studies[10,18] showed that female more than male patients on DTG-based antiretroviral therapy were associated with neuropsychiatric ADEs, our findings revealed the opposite that more males than female patients experienced neuropsychiatric ADEs, however, the association was not statistically significant ($p = 0.4455$). Moreover, hypersensitivity-like and some systemic ADEs showed statistically significant association with sex and age, respectively (Table 4).

Patients react differently to drugs. While some patients would tolerate a drug very well, others encounter serious adverse events and reactions to the same drug. ADEs have substantial negative effects on the patients' quality of life, socioeconomic productivity (e.g. time away from work, etc.), lowers patient satisfaction as well as affecting adherence to treatment[23,24]. Importantly, ADEs impact on the health system as they tend to increase hospital admissions, prolong hospital stay, with additional resource requirements and utilisation of health human resource, pharmaceutical supplies and equipment to manage patients[25]. It would be interesting to quantify the costs and additional resource utilisation involved in managing ADEs associated with HIV treatment in Zambia. These are potentially studies for the future. Either way, the substantial costs and additional resource requirements ADEs impose on the national health system that is already faced with limited resources justify investment in preventive efforts to avoid their occurrence. Robust and active surveillance, reporting and causality assessment to generate signals for regulatory action are such strategies

worth investing in to strengthen in the health system. Our findings reveal that whereas some ADEs experienced by patients initiated on DTG-based regimen are preventable and ameliorable, some are perhaps non-preventable. Moreover, studies are required to describe the incidence, severity, and preventability of ADEs affecting various populations of patients, including paediatrics and pregnant women on HIV treatment. We agree with Foster and colleague's argument that enhanced ADE reporting will help the national health system delineate preventable ADEs - judged to have been caused by medication errors; ameliorable ADEs – those whose severity could be decreased in the population; and non-preventable ADEs – those due to a medication where there is no error in the medication process[23].

IMPLICATIONS OF THE FINDINGS

This study brings out preliminary information from the Zambian setting about reported ADEs and other safety concerns being experienced by patients on DTG-based treatment. On the merit of this data, it was noteworthy that although some of the frequently reported ADEs such as headaches, dizziness, insomnia, diarrhoea, nausea that were reported among Zambian patients on DTG-based regimen were in consonant with some of the side effects listed in the product package insert by the manufacturer as frequently occurring (1 – 10%) and some such as hypersensitivity reactions less commonly occurring (0.1 – 1%), our findings placed emphasis on the severity and outcomes of these effects on the patient.

Taken together, findings of this study show preliminary evidence that patients on DTG-based antiretroviral regimen for HIV treatment in Zambia experienced ADEs among which central nervous system effects were prevalent. Of concern was that a number of these ADEs experienced were associated with morbidity and discontinuation of DTG-based regimen among HIV patients. Whether the discontinuation was subject to re-challenge or de-challenge was subject to further elucidation in subsequent studies. Furthermore, longitudinal and cohort studies are required to explore other safety, clinical and pharmacological parameters of DTG-based regimens used for HIV treatment in Zambia and other settings where DTG has been introduced. It will be interesting to also explore and elucidate causal relationships, including possible mechanisms by which DTG induces adverse effects in the human body systems. Our findings serve to not only confirm safety information about this drug but to also steer up further studies to improve medication safety and clinical care. Zambia's national pharmacovigilance system has shown the capability to monitor drug safety of HIV drugs except that the systems and strategies employed need to be strengthened and supported.

LIMITATIONS AND FUTURE WORK

Our findings relied on the analysis of secondary data from reported incidents of ADEs submitted to ZAMRA using the official reporting channels. Incidence rates could not be determined as the dataset was not representative of all HIV patients initiated on DTG-based combination treatment. An incident can occur at any point in the medication use process and might represent an ADE, potential ADE, medication error, or none of these as it is essentially a "catch-all" term for what to call something before it has been classified[11]. Due to the retrospective and non-detailed nature of the case reports, other clinically relevant variables were not available for consideration. Causality was not ascertained. Future studies will do well to consider collecting clinical and patient-specific data, including other medications the patient was taking.

CONCLUSION

Neurological and neuropsychiatric effects were commonly experienced ADEs among patients initiated on DTG-based antiretroviral regimen in Zambia. ADEs were frequently experienced more in males and older patients, respectively. A number of the ADEs experienced were associated with morbidity and discontinuation of DTG-based regimen among HIV patients. Notwithstanding, the

rates of ADE reporting among patients and healthcare providers remained relatively low and must be addressed for ZAMRA to address medication safety concerns going forward.

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Conflict of interest

Authors declare no conflict of interest associated with this work. This work was not funded.

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