Prevalence and Factors Associated With Adverse Drug Events Among Patients On Dolutegravir-Based Regimen At The Immune Suppression Syndrome Clinic of Mbarara Regional Referral Hospital, Uganda: A Retrospective Cross-Sectional Study.

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Research

Keywords: DTG-based ART, Adverse drug events, HIV, Uganda

Posted Date: October 28th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1007649/v1

TITLE PAGE

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Abstract

Background: Highly Active Antiretroviral Therapy is efficacious in suppression of Human Immunodeficiency Virus (HIV) however, it is associated with numerous toxicities hence great effort has been put into development of antiretrovirals with better tolerability. The World Health Organization recommended dolutegravir as first-line antiretroviral therapy however, recent studies have raised concerns regarding its safety in real-clinical settings due to adverse drug reactions (ADEs). Hence the purpose of this study was to establish the prevalence and factors associated with adverse drug events among patients on dolutegravir-based regimen at the Immune Suppression Syndrome (ISS) Clinic- Mbarara Regional Referral Hospital (MRRH).

Methods: A retrospective cross-sectional study was conducted at ISS Clinic-MRRH among 375 randomly selected patients who had been exposed to DTG-based regimen for at least 12 weeks. The patients were interviewed to obtain data on sociodemographics, dietary habits and thereafter their files reviewed to obtain data on ADEs. Data entry was done using Epi-data 3.0 and exported to SPSS version 25.0 for analysis. The prevalence of ADEs was determined as a percentage, and ADE associated factors were assessed using bivariate analysis, those found significant were further subjected to multivariate logistic regression model and were considered significant at $P<0.05$.

Results: The prevalence of adverse drug events among patients on DTG-based regimen was found to be 33.1% (124/375) with 5.6% (7/124) participants discontinued from treatment due ADEs, 4 of which were due to hyperglycemia and 3 due to liver toxicity. The commonly experienced ADEs included abdominal pain, hyperglycemia and liver toxicity each at 7.3%, headache at 11.3%, and allergy at 36.3%. Male sex (AOR 1.571, 95% CI 1.433- 1.984), WHO stage one at entry to care (AOR 4.586, 95% CI 1.649-12.754), stage two (AOR 4.536, 95% CI 1.611-12.776), stage three (AOR 3.638, 95% CI 1.262-10.488), were significantly associated with ADEs. Patients with

undetectable viral load at initiation of DTG-based regimen were less likely to experience ADEs (AOR = .324, 95% CI .1167-.629).

Conclusions: Up to a third of patients on DTG-based regimen experienced ADEs. Male sex, WHO HIV disease stage and a detectable viral load at initiation of DTG-based regimen were significantly associated with ADEs. It is crucial to actively monitor patients with these characteristics for ADEs.

Keywords: DTG-based ART, Adverse drug events, HIV, Uganda.

Background

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDs) still remain a major challenge in the health sector. Globally, 38 million people were living with HIV in 2019. In Uganda it is estimated that 1.4 million people were living with HIV/AIDs by 2018, an adult HIV prevalence of 5.7%, with 73% of adults and 66% of children enrolled on antiretroviral treatment [1,2].

Over the years, antiretroviral treatment has evolved to Highly Active Antiretroviral Therapy (HAART) regimens that include a combination of drugs that are more efficacious and have significantly reduced HIV/AIDs- related morbidity and mortality [3,4]. However, HAART is associated with numerous toxicities ranging from mild to fatal [5]. In 2018, the Uganda National Drug Authority (NDA), reported that 44.9% of all reported adverse drug reactions were associated with antiretroviral drugs (ARVs) [6].

Adverse drug events affect therapeutic outcomes of HAART by leading to non-adherence and therapy discontinuation [7,8]. Unfortunately, up to 28.9% of patients on HAART are non-compliant to their medications, with 25% dropping off their initial regimens within the first eight months due to ADEs [9]. This has far reaching implications including; treatment failure, necessitating change to more expensive therapy, development of drug resistance and ultimately increased mortality [10]. Great effort has been put into development of new antiretroviral drugs with better tolerability and consequently, it is crucial to constantly monitor for new developing adverse drug events [11].

Following World Health Organization (WHO) recommendations in 2018, dolutegravir (DTG)-based antiretroviral therapy was adopted as first line treatment for all PLWHIVA, dolutegravir an

integrase inhibitor, is combined with two nucleoside/ tide reverse transcriptase inhibitors (NRTI) usually abacavir/lamivudine or tenofovir/lamivudine [12,13].

In Uganda, dolutegravir-based regimen was included as first line antiretroviral therapy in the consolidated guidelines for the prevention and treatment of HIV in September 2018 [14]. Subsequently, in November 2018, the Immune Suppression Syndrome (ISS) clinic of Mbarara Regional Referral Hospital (MRRH) included DTG-based regimen in the HAART programme as first line therapy [14].

The prevalence of adverse drug events among patients on DTG-based antiretroviral therapy in a study conducted in Europe by was reported at 3.6% (70/1950) [13].

Patients on DTG-based regimen may experience adverse drug events including nausea, vomiting, diarrhea, allergies, rash, headache, insomnia, hepatotoxicity and hyperglycemia among others [13,15].

Studies have reported various factors associated with adverse drug events among patients on DTG-based regimen, among which include female sex and age at entry into study [13,16].

Clinical trials conducted on dolutegravir-based regimen reported frequency of occurrence of adverse drug events of 2%, however recent studies in real clinical settings have reported a much higher frequency of up to 10% [15,18]. In a study by de Boer et al., 13.7% patients were discontinued from DTG-based regimen due to adverse drug events [17]. In a study by Bofanti et al., 5.4% participants were discontinued from DTG-based therapy due to adverse drug events [16]. A study conducted in Uganda at the Infectious Disease Institute also reported adverse drug events among patients taking dolutegravir-based antiretroviral therapy [19]. There is limited information on the adverse drug events of DTG-based regimen in real clinical settings in sub-Saharan Africa

and Uganda, hence there is need to continuously monitor this novel treatment for adverse drug events.

Therefore, this study aimed to determine the prevalence and associated factors of adverse drug events among patients on dolutegravir-based regimen at the Immune Suppression Syndrome Clinic- Mbarara Regional Referral Hospital.

Methods

Study design

This research was a retrospective cross-sectional study involving patients in HIV care at the Immune Suppression Syndrome Clinic of Mbarara Regional Referral Hospital, Uganda who had been exposed to dolutegravir-based antiretroviral therapy for at least 12 weeks. The objectives of the study included; (1) to determine the prevalence of adverse drug events, (2) to identify adverse drug events experienced and (3) to establish factors associated with adverse drug events among patients on dolutegravir-based regimen at the Immune Suppression Syndrome Clinic of Mbarara Regional Referral Hospital.

The ethical considerations of this study were approved by Mbarara University of Science and Technology Research Ethics Committee (MUST-REC) approval number, MUREC 1/9 02/12-19, and Faculty of Medicine through the Faculty Research Committee (FRC) approval number DMS 6.

Study Setting

This study was conducted at the Immune Suppression Syndrome (ISS) Clinic of the Mbarara Regional Referral Hospital (MRRH), a government-aided hospital located in Mbarara district in

the South western region of Uganda. The facility majorly serves patients from South-Western districts of Uganda including Buhweju, Bushenyi, Ibanda, Isingiro, Kazo, Kiruhura, Mitooma, Ntugamo, Mbarara, Rubirizi, and Rwampara among others. Currently, the ISS clinic serves a total number of 21,600 patients; 11,600 pediatric and 10,000 adults. The facility has an average daily attendance of 300 patients. The ISS clinic provides services including; HIV counselling and testing, elimination of mother to child transmission of HIV (EMTCT), HIV care, treatment and support for people living with HIV/AIDs including children, adolescents and adults.

Study population and sample

The study population consisted of both male and female patients aged 20 years and above at the time of initiation of dolutegravir-based HAART regimen and had been on the regimen for at least 12 weeks at the Immune Suppression Syndrome Clinic of Mbarara Regional Referral Hospital, Uganda.

The sample size of 375 patients was determined using the Slovin's formula [18] based on the total population of patients who were on dolutegravir-based ART regimen at ISS clinic.

Unique identification codes for patients who were eligible to participate in the study were run through Microsoft excel and a sample size of 375 was generated by random draw method. An appointment list was used to identify when the patients attended clinic visit, upon which they were asked to consent and participated in the study. The method eliminated bias, provided an equal chance to every eligible patient to be selected for the study and patients participated on their official clinic appointment day.

Written and informed consent was obtained from the patients to participate in the study and to use their files for obtaining data for the study. Before participants signed consent forms, they were

informed that participation was voluntary and they could drop out at any time, the purpose, objectives, possible benefits and risks of the study were clearly explained and only patient identification numbers were used which maintained utmost confidentiality.

Data collection tool and procedures

Selected patients were interviewed and there-after their medical files were reviewed and data on ADEs was obtained from the ART cards as recorded by clinicians. The data collection tool consisted of two sections; The first section was completed through patient interview and collected information on social demographics including; sex, age, marital status, religious affiliation, level of education and employment status, types of meals consumed before swallowing medicine, if patients received counselling instructions to follow while taking the regimen and time the medicine is taken.

The second section was completed by file review and collected data on duration since HIV diagnosis, CD4 at entry into care, duration on HAART, viral load at initiation of dolutegravir-based regimen, previous ART regimen, body mass index, recorded adverse drug event since start of dolutegravir-based regimen, any treatment modification; discontinuation, comorbidities, other medications, blood glucose measurements and liver function tests.

The data abstraction form for each patient/file were assigned an identification code. The filled forms were checked for accuracy, consistency and completeness by the principal investigator. Completed forms were kept under restricted access which protected patient confidentiality and protected data from alteration.

The first section of the data collection tool was translated to Runyankole the commonly used local language.

Statistical analysis

All filled data collection forms were checked, coded and data entry done using Epi data. Data cleaning and validation was done to detect any errors. The data was then exported and analyzed using a statistical package for social sciences (SPSS) version 25.0. Socio-demographics were presented using descriptive statistics; mean and standard deviation and categorical variables were presented using frequencies, proportions and percentages. The data was presented using text, tables, and graphs. Prevalence of ADEs was determined by obtaining the number of patients in the sample who had at least one ADE recorded in their medical file on the ART card divided by the total number of the sample size. This was expressed as a percentage.

Adverse drug events experienced by patients were captured from ART cards in the medical files as recorded by clinicians. Severity rating of ADEs was based on the DAIDS grading of ADEs using data from medical files. ADEs were graded as mild if symptoms caused no or minimal interference with usual social activities with intervention not indicated, moderate if symptoms caused greater than minimal interference with usual social and functional activities with interventions indicated, severe if symptoms caused inability to perform usual social and functional activities with intervention or hospitalization indicated and potentially life threatening if symptoms caused inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death. This data was presented in form of frequencies, percentages, and proportions in graphs, charts and tables.

The relationship between factors associated with adverse drug events to dolutegravir-based regimen was established using bivariate analysis. Variables found significant at bivariate level were then subjected to multivariate analysis. Variables were considered statistically significant if p-value was less than 0.05 measured with odds ratio at 95% confidence interval.

Results

Characteristics of study participants

Most of the study participants were male 59.5% (223/375), with majority of respondents in the age bracket of 40-49 years and 50-59 years consisting of 34.1% (128/375) each, with median age 49years interquartile range 12. Participants who had been on HAART for 5-10 years were 78.9% (296/375), 77.9% (292/375) of the participants had undetectable viral loads at the time of initiation of DTG-based regimen, and all the participants were in WHO stage one at initiation of DTG-based regimen. (Table 1).

Table 1 Social demographic characteristics of study participants

Variables	Category	Frequency (n=375)	Percentage (%)
Sex	Male	223	59.5
	Female	152	40.5
Age	20-29 years	16	4.3
	30-39 years	55	14.7
	40-49 years	128	34.1
	50-59 years	128	34.1
	≥60 years	48	12.8
Marital status	Single	57	15.2
	Married	219	58.4
	Separated/Divorced	36	9.6

	Widow/widower	63	16.8
Religious affiliation	Catholics	119	31.7
	Anglican	205	54.7
	Muslims	31	8.3
	Other	20	5.3
Highest education level	No formal education	43	11.5
	Primary	184	49.1
	'O'level	91	24.2
	'A'level	18	4.8
	Tertiary	39	10.4
Employment status	Employed	282	75.2
	Unemployed	93	24.8

n number of participants

Prevalence of ADEs

One third (33.1%, 124/375) of the respondents had at least one ADE recorded in their files since initiation of DTG-based regimen.

ADEs experienced by study participants

The commonly recorded ADEs included; abdominal pain, hyperglycemia and hepatotoxicity each at 7.3%, paresthesia at 8.1%, headache at 11.3%allergy at 36.3%. (See Table 2 on page 9)

Using the DAIDs grading of adverse drug events, of the 7.3% (9/124) patients who experienced hyperglycemia, five had grade 1, two had grade 2, one with grade 3 and one with grade 4, this was reported between 13-62 weeks of starting the DTG-based regimen. (See Table 3 on page 10)

Of the 7.3% (9/124) patients who experienced liver toxicity; eight had grade one and one had grade 4, this was reported between 15-63 weeks of starting the DTG-based regimen. All the patients who experienced liver toxicity were concomitantly taking isoniazid preventive therapy. (See Table 4 on page 10)

As result of ADEs 5.6% (7/124) participants were discontinued from DTG-based regimen, 4 due to hyperglycemia and 3 due to liver toxicity.

Table 2 Commonly experienced ADEs by study participants.

ADE	Number of participants with ADE recorded	Percentage (%)
Allergy	45	36.3
Bone/Joint/Muscle pain	17	13.7
Headache	14	11.3
Skin rash	11	8.9
Paresthesia	10	8.1
Hyperglycemia	9	7.3
Abdominal Pain	9	7.3
Liver toxicity	9	7.3
Insomnia	7	5.6
Diarrhea	5	4
Renal Toxicity	3	2.4
Dizziness	2	1.6
Nausea	1	0.8
Malaise	1	0.8

Sleep disturbances	1	0.8
Fever	1	0.8
Anxiety	1	0.8

224 % (number of participants with ADE recorded/ total number of participants with at least one ADE
225 recorded in their medical files).

226 **Table 3** Grading of hyperglycemia and duration on DTG-based regimen at time of ADE
227 identification [29]

#	RBS mmol/L	DAIDS Grade	Start date of DTG-based regimen	Date ADE was 1st recorded	No. of weeks on DTG-based ART at time of ADE identification
1	8.3	1	01/10/2019	17/03/2020	24.0
2	30.8	4	24/04/2019	23/10/2019	26.0
3	8.7	1	03/01/2019	10/03/2020	61.7
4	9.7	2	28/05/2019	12/03/2020	41.3
5	8.1	1	19/02/2019	12/03/2020	55.3
6	18.9	3	21/03/2019	12/03/2020	51.0
7	7.8	1	18/12/2018	19/11/2019	48.0
8	7.8	1	10/12/2019	10/03/2020	13.0
9	8.9	2	20/06/2019	27/02/2020	36.0

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Table 4: Grading of liver toxicity and duration on DTG-based regimen at time of ADE identification [29]

#	AST(IU/L)	ALT(IU/L)	DAIDS Grade	Start date of DTG-based regimen	Date ADE was 1st recorded	No. of weeks on DTG-based ART at time of ADE identification
1	48	45	1	09/01/2019	02/10/2019	38.0
2	984.5	583.1	4	13/11/2018	05/11/2019	51.0
3	47	49	1	15/01/2019	10/12/2019	47.0
4	53	61	1	22/05/2019	21/10/2019	21.7
5	46.4	50.9	1	26/02/2019	02/08/2019	22.4
6	44	43	1	07/03/2019	02/03/2020	51.6
7	45.4	35.9	1	18/03/2019	17/10/2019	30.4
8	45	26	1	20/03/2019	08/07/2019	15.7
9	47	50	1	20/12/2018	02/03/2020	62.6

Factors associated with ADEs

At bivariate analysis male sex (Crude OR=1.789, 95% CI 1.156- 2.768), being in the age bracket of 30-39 years (Crude OR=2.621, 95% CI 1.089-6.307), being married (Crude OR=2.627, 95% CI 1.475-4.679) and being employed (Crude OR=1.674, 95% CI 1.032-2.716), eating non-fatty meals before swallowing the medicines (Crude OR=0.571, 95% CI .335-.976), duration of HIV diagnosis

of less than 5 years (Crude OR=1.789, 95% CI 1.156- 2.768), having HIV for 5-10 years since diagnosis (Crude OR=3.417, 95% CI 1.327-8.795), being in WHO stage one at entry into care (Crude OR=4.472, 95% CI 1.757-11.386), being in WHO stage two at entry into care (Crude OR=4.000, 95% CI 1.539-10.396), being in WHO stage three at entry into care (Crude OR=2.800, 95% CI 1.050-7.469), having undetectable viral load at initiation of DTG (Crude OR=.336, 95% CI .180-.625), were significantly associated with ADE among patients on DTG-based regimen. (see Table 5 on page 19).

At multivariate analysis, all variables found significant at bivariate analysis were considered. Male sex (Adjusted OR=1.571, 95% CI 1.433- 1.984), being in WHO stage one at entry to care had (AOR =4.586, 95% CI 1.649-12.754) WHO stage two (AOR =4.536, 95% CI 1.611-12.776), WHO stage three (AOR =3.638, 95% CI 1.262-10.488), and viral load at initiation of DTG-based regimen were significantly associated with ADEs among patients on DTG-based regimen. Patients with undetectable viral load at DTG-regimen initiation (AOR = .324, 95% CI .1167-.629) were less likely to experience ADEs. (See Table 6 on page 12)

Table 6 Multivariate analysis of factors associated with adverse drug events among patients on dolutegravir-based regimen

Variable	**Category**	**Crude OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Sex	Male	1.789(1.156- 2.768)	.009	1.571 (1.433-1.984)	.031
	Female	1.0		1.0	
WHO staging at entry to care	Stage one	4.472(1.757-11.386)	.002	4.586(1.649-12.754)	.004*
	Stage two	4.000(1.539-10.396)	.004	4.536(1.611-12.776)	.004*

	Stage three	2.800(1.050-7.469)	.040	3.638(1.262-10.488)	.017*
	Stage four	1.0		1.0	
Viral load at initiation of DTG	Undetectable	.336(.180-.625)	.001	.324(.1167-.629)	.001*
	Detectable			1.0	

**-significance, less than 0.05*

Discussion

The prevalence of ADEs among patients on DTG-based regimen at the ISS Clinic-MRRH was 33.1% (124/375). The commonly experienced ADEs included abdominal pain, hyperglycemia, hepatotoxicity each at 7.3%, headache at 11.3% and allergy at 36.3%. Most ADEs (65.5%) were rated as moderate while 29.7% were mild, 3.4% were severe and 1.4% were potentially life threatening. As result of ADEs 5.6% (7/124) participants were discontinued from DTG-based regimen. Male sex (Adjusted OR=1.571, 95% CI 1.433- 1.984), being in WHO stage one at entry to care had (AOR =4.586, 95% CI 1.649-12.754) WHO stage two (AOR =4.536, 95% CI 1.611-12.776), WHO stage three (AOR =3.638, 95% CI 1.262-10.488), and viral load at initiation of DTG-based regimen were significantly associated with ADEs among patients on DTG-based regimen. Patients with an undetectable viral load (AOR = .324, 95% CI .1167-.629) were less likely to experience ADE.

The study found that the prevalence of adverse drug events among HIV patient on dolutegravir-based regimen was 33.1% (124/375) which is comparable to 32% (N=297) reported by Nabitaka, et al., in a study conducted in Uganda to assess the acceptability and viral suppression of DTG-based first-line ART [20]. The current study ADE prevalence is however higher than 10.4% (23/223) reported by reported Correa, et al., [18], in a study conducted in Brazil and also differs from the 3.6% (70/1950) reported by a study conducted in Switzerland by Elzi, et al., [13]. A

possible explanation for higher prevalence might be due to the small number of patients who participated in this study compared to those in the Elzi, et al., study which may contribute to over estimation of the ADEs.

The study found that 5.6% of ADEs resulted in discontinuation of DTG-based regimen which is comparable to 5.4% patients whose treatment on a DTG-based regimen was interrupted due to an ADEs in an Italian cohort study [16], however, lower than 13.7% reported as the discontinuation rate for DTG-based regimen due to ADEs by de Boer, et al., [17]. This could be because of differences in patient characteristics between the current study and the de Boer, et al., study. The current study had patients majorly on tenofovir/lamivudine/dolutegravir whereas the de Boer, et al., study, had less patients on tenofovir/lamivudine/dolutegravir and the majority on abacavir/lamivudine/dolutegravir in which more treatment discontinuations were observed hence contributing to a higher discontinuation rate.

The study found out that allergy was the most commonly recorded ADE at 36.3% (45/124) much higher than the 5.3% (4/75) reported by Elzi, et al., [13] and 0.8% as observed by Menard, et al., [21]. This could be because of differences in the characteristics of the study populations.

The study found that headache was the most common neuropsychiatric ADE recorded at 11.3% (14/124) comparable to 12.9% (8/56) reported in a study in Netherland by Kees, et al., [22]. However higher than 1.6% (16/985) that was reported as the percentage of patients who experienced headache as an adverse drug event in a study by Hoffman, et al., [15] and 4.3% (1/23) reported by Correa, et al., [18]. The difference could be because of the fewer number of patients involved in the current study compared to those in the study by Hoffman, et al., hence over estimation of ADE and the study by Correa, et al., involved only patients who were on DTG-based

regimen as initial ART therapy whereas this study involved both patients who had been already exposed other ART regimen and those who were on DTG-based regimen as initial ART therapy.

In the study, the gastrointestinal ADE mainly reported was abdominal pain at 7.3% (9/124) which is higher than 3.8% (21/556) reported by de Boer, et al., [17] but lower than 25% (19/75) reported by Elzi et al., [13] but this could be because in the study had fewer patient numbers in comparison to the study by de Boer, et al., resulting to over estimation of the ADEs. The study results were different from Elzi, et al., findings probably due to difference in study populations.

The current study reported hyperglycemia at 7.3% (9/124) in contrast to results reported in a study conducted in Uganda by Lamorde, et al., [19], new-onset hyperglycemia at 0.47% (16/3417) patients in the case group vs 0.03% (1/3230) in the control group. The difference could be because the current study involved fewer number of patients leading to over estimation of ADE. Antiretroviral therapy is associated with insulin resistance through two major mechanisms including; interference with insulin signaling at the cellular level and defects in lipid metabolism that result in obesity [23]. Patients taking DTG-based regimen may develop insulin resistance which may result in increased blood glucose levels.

This study reported liver toxicity occurred in 7.3% (9/124) patients, all of whom were concomitantly taking isoniazid at time of experiencing ADE, this is comparable with 9.3% (7/75) reported as the percentage of patients who experience liver toxicity in a study by Elzi, et al., [13]. Co-administration of DTG-based therapy and isoniazid results in significantly elevated levels of inflammatory markers such as c-reactive protein, interferon-γ, CXCL10, and other cytokines which result into liver toxicity as an ADE [24]. Liver toxicity can also occur in patients on DTG-based therapy who have untreated hepatic B or C [25,26].

316 The study found that male sex was significantly associated with adverse drug events among HIV
317 patient on dolutegravir-based regimen (Adjusted OR=1.571, 95% CI 1.433- 1.984). This is
318 contrary to findings by Elzi, et al., [13] who found female sex to be significantly associated with
319 adverse drug event at multivariate analysis (HR 1.98, 95% CI 1.45–2.71, P<0.001). The difference
320 in the study findings could probably because of genetic and physiological variations in study
321 populations.
322 In this study, WHO staging at entry was significantly associated with adverse drug event among
323 HIV patient on dolutegravir-based regimen. Participants being in WHO stage one at entry to care
324 had (AOR =4.586, 95% CI 1.649-12.754), those in WHO stage two (AOR =4.536, 95% CI 1.611-
325 12.776) and those in WHO stage three (AOR =3.638, 95% CI 1.262-10.488). In contrast a study
326 by Kindie, et al., [27] conducted on assess factors associated with ADEs among patients on
327 antiretroviral regimen including tenofovir/lamivudine/efavirenz, abacavir/lamivudine/efavirenz,
328 and zidovudine/lamivudine/nevirapine, it was found that the risks in WHO clinical stage II, III, IV
329 were much higher than stage I (AHR 4, 95% CI: 1.33-11.93, AHR 5.3, 9.5% CI: 2.02-13.79 and
330 AHR 7, 95% CI: 2.51-20.10) respectively. The difference in findings in probably because of
331 variation in study population characteristics.
332 Another factor significantly associated with adverse drug events among HIV patient on DTG-
333 based regimen was viral load count at initiation of DTG-based regimen. Patients who had
334 undetectable viral load at initiation of DTG-based regimen (AOR = .324, 95% CI .1167-.629),
335 were 67.6% less likely to have ADEs compared to those who had a detectable viral load at the
336 initiation of DTG-based regimen. This is probably because patients with undetectable viral load
337 count have a better immunity hence are less susceptible to experiencing ADEs whereas those with
338 a higher viral load count have compromised immunity and are more susceptible to experiencing

ADEs. A prospective cohort study conducted to assess risk factors associated with occurrence of ADEs among HIV-infected adults on protease inhibitor containing ART regimen also found out that a higher viral load at start of the ART regimen was associated with occurrence of ADEs (HR 1.5; 95% CI, 1.1-2.2). [28].

Conclusion

This study reports a high prevalence of ADEs among patients on DTG-based regimen, up to a third of the patients experienced ADEs. Male sex, WHO HIV disease stage and a detectable viral load at initiation of DTG-based regimen were significantly associated with ADEs. It is crucial to actively monitor patients with these characteristics for ADEs.

Study Limitations

The study used already existing records of which some had missing information and inaccuracies in data capturing.

Existing laboratory results on blood glucose tests and liver function tests were used to capture laboratory data on adverse drug events such as hyperglycemia and liver toxicity however most patient files did not have these test results.

Recommendations

In addition to the pre-monitoring guidance for initiating DTG-based regimen as stipulated in consolidated guidelines for the prevention and treatment of HIV in Uganda, the Government of Uganda, through Ministry of Health and National Medical Stores should provide the necessary equipment and supplies to enable implementation and conducting of baseline blood sugar and liver function tests for all patients before initiating DTG-based regimen.

Regular screening for ADEs and periodic laboratory monitoring of blood glucose and liver function tests for patients who have been initiated on DTG-based ART regimens especially in the third month (13 weeks) of starting therapy and 16 months (63 weeks) of DTG-based therapy.

Area for further study

This study recommends a further large-scale prospective cohort study to assess the magnitude and associated factors for ADEs by using clinical and laboratory examination, and a study on ADEs among patients on DTG-based ART regimen and isoniazid preventive therapy.

382 **Table 3** Bivariate of factors associated with adverse drug reactions among patients on
383 dolutegravir-based regimen

Variables	**Category**	**Recorded experience of ADR**		**Crude OR (95% CI)**	**p-value**
		Yes (%)	No (%)		
Sex	Male	62(50.0)	161(64.1)	1.789(1.156- 2.768)	**.009***
	Female	62(50.0)	90(35.9)	1.0	
Age	20-29 years	5(4.0)	11(4.4)	1.441(.432-4.810)	.552
	30-39 years	11(8.9)	44(17.5)	2.621(1.089-6.307)	.032*
	40-49 years	44(35.5)	84(33.5)	1.251(.631-2.478)	.521
	50-59 years	45(36.3)	83(33.1)	1.208(.610-2.392)	.587
	≥60 years	19(15.3)	29(11.6)	1.0	
Marital status	Single	22(17.7)	35(13.9)	1.541(.745-3.188)	.243
	Married	59(47.6)	160(63.7)	2.627(1.475-4.679)	**.001***
	Separated/Divorced	12(9.7)	24(9.6)	1.938(.827-4.537)	.128
	Widow/widower	31(25.0)	32(12.7)	1.0	
Religious affiliation	Catholics	40(32.3)	79(31.5)	1.616(.619-4.218)	.327
	Anglican	63(50.8)	142(56.6)	1.844(.728-4.672)	.197
	Muslims	12(9.7)	19(7.6)	1.295(.415-4.048)	.656
	Other	9(7.3)	11(4.4)	1.0	
Highest education level	No formal education	16(12.9)	27(10.8)	.506(.192-1.333)	.168
	Primary	59(47.6)	125(49.8)	.636(.284-1.424)	.271

	'O' level	32(25.8)	59(23.5)	.553(.234-1.307)	.177
	'A' level	8(6.5)	10(4.0)	.375(.114-1.234)	.107
	Tertiary	9(7.3)	30(12.0)	1.0	
Employment status	Employed	85(68.5)	197(78.5)	1.674(1.032-2.716)	**.037***
	Unemployed	39(31.5)	54(21.5)	1.0	
Receive counselling instructions to follow while taking the regimen	Yes	106(85.5)	229(91.2)	1.768(.910-3.434)	.093
	No	18(14.5)	22(8.8)	1.0	
Amount of daily intake of water	Less than 3 litres	86(69.4)	180(71.7)	1.221(.602-2.477)	.580
	Average 3 litres	24(19.4)	47(18.7)	1.142(.502-2.600)	.751
	More than 3 litres	14(11.3)	24(9.6)	1.0	
Frequency of eating vegetables in a week	Never Once	11(8.9) 21(16.9)	26(10.4) 43(17.1)	1.206(.565-2.576) 1.045(.578-1.889)	.628 .884
	Twice	18(14.5)	37(14.7)	1.049(.559-1.968)	.881
	3 and more times	74(59.7)	145(57.8)	1.0	
Time for taking medicine	Morning	101(81.5)	221(88.0)	1.678(.928-3.032)	.087
	Evening	23(18.5)	30(12.0)	1.0	
Meals eaten before	Non-fatty meals	35(28.2)	50(19.9)	.571(.335-.976)	**.040***

swallowing medicines	Plant based fatty meals	11(8.9)	22(8.8)	.800(.363-1.762)	**.580**
	Animal based fatty meals	24(19.4)	44(17.5)	.733(.407-1.322)	**.302**
	Both plant and animal based fatty meals	54(43.5)	135(53.8)	1.0	
Duration since HIV diagnosis	<5 years	12(9.7)	41(16.3)	3.417(1.327-8.795)	**.011***
	5-10 years	27(21.8)	93(37.1)	3.444(1.525-7.779)	**.003***
	11-15 year	69(55.6)	101(40.2)	1.464(.686-3.122)	.324
	>15 years	16(12.9)	16(6.4)	1.0	
CD4 at entry into care	<500	99(79.8)	204(81.3)	1.096(.638-1.883)	.740
	≥500	25(20.2)	47(18.7)	1.0	
Who staging at entry into care	Stage one	45(36.3)	115(45.8)	4.472(1.757-11.386)	**.002***
	Stage two	35(28.2)	80(31.9)	4.000(1.539-10.396)	**.004***
	Stage three	30(24.2)	48(19.1)	2.800(1.050-7.469)	**.040***
	Stage four	14(11.3)	8(3.2)	1.0	
Duration on HAART	<5 years	16(12.9)	51(20.3)	1.912(.411-8.900)	.409
	5-10 years	102(82.3)	194(77.3)	1.141(.267-4.871)	.858
	11-15 year	3(2.4)	1(.4)	.200(.014-2.911)	.239

	>15 years	3(2.4)	5(2.0)	1.0	
Viral load at initiation of DTG	Undetectable	110(88.7)	182(72.5)	.336(.180-.625)	**.001***
	Detectable	14(11.3)	69(27.5)	1.0	
Previous ART Regimen	AZT/3TC/EFV	23(18.5)	44(17.5)	1.366(.390- 4.786)	.625
	AZT/3TC/NVP	50(40.3)	82(32.7)	1.171(.353- 3.890)	.796
	TDF/3TC/EFV	40(32.3)	112(44.6)	2.000(.601- 6.661)	.259
	TDF/3TC/NVP	6(4.8)	6(2.4)	.714(.143- 3.579)	.682
	N/A	5(4.0)	7(2.8)	1.0	
BMI assessment	Underweight	15(12.1)	7(2.8)	.467(.075-2.923)	.416
	Normal weight	83(66.9)	188(74.9)	2.265(.448-11.457)	.323
	Overweight	18(14.5)	45(17.9)	2.500(.461-13.563)	.288
	Obese Class I	5(4.0)	8(3.2)	1.600(.227-11.266)	.637
	Obese Class II	3(2.4)	3(1.2)	1.0	
Patient have any comorbidities at time of experiencing ADE	Yes	20(16.1)	43(17.1)	1.075(.602- 1.921)	.807
	No	104(83.9)	208(82.9)	1.0	

**-significance, less than 0.05.*

List of abbreviations

ADEs	Adverse Drug Events
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARVs	Antiretrovirals
AST	Aspartate aminotransferase
DAIDS	Division of Acquired Immunodeficiency Syndrome
DTG	Dolutegravir
FRC	Faculty Research Committee
GIT	Gastrointestinal
HAART	Highly Active Anti-Retroviral Treatment
HIV	Human Immunodeficiency Virus
INH	Isoniazid
ISS	Immune Suppression Syndrome
IRB	Institutional review board
MOH	Ministry of Health
MRRH	Mbarara Regional Referral Hospital

MUST	Mbarara University of Science and Technology
NDA	National Drug Authority
NP-AEs	Neuropsychiatric adverse events
PLWH	People Living With HIV
REC	Research Ethics Committee
SPSS	Statistical package for social sciences
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Health Organization

Declarations

Ethical approval and consent to participate

The ethical considerations of this study were approved by Mbarara University of Science and Technology Research Ethics Committee (MUST-REC) approval number, MUREC 1/9 02/12-19, and Faculty of Medicine through the Faculty Research Committee (FRC) approval number DMS 6. Written and informed consent was obtained from the patients to participate in the study and to use their files for obtaining data for the study. Before participants signed consent forms, they were informed that participation was voluntary and they could drop out at any time, the purpose, objectives, possible benefits and risks of the study were clearly explained and only patient identification numbers were used which maintained utmost confidentiality. Consent for publication was not sought as it is inapplicable since no individual's participant's data were reported in the article in any form such as videos, images or voice recordings.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

The first author received a Pharmbiotrac Scholarship to support her Master's study. This study has not received any financial support for publication charges.

Authors' contributions

AN was responsible for the design, data collection, analysis and interpretation, and drafting of the manuscript. JHW, WM, RT, and OJ participated in the study design and provided supervision and assistance towards data analysis, interpretation, and critically revising the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank all the study participants for their participation in this study. We acknowledge the management, staff of the Immune Suppression Syndrome Clinic – Mbarara Regional Referral Hospital and the data manager Mr. Kanyesigye Michael for assistance in data collection and analysis. We thank Namuleme M. Lorna and Mr. Semakula Tebusweke for all their support.

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