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Prevalence and factors associated with hyperglycemia among persons living with HIV/AIDS on dolutegravir-based antiretroviral therapy in Uganda

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Abstract

Background: Dolutegravir-based (DTG) regimens are rapidly becoming the preferred first-line antiretroviral therapy (ART) for people living with HIV (PLHIV) in low and middle-income countries. However, there are rising concerns over the development of hyperglycemia and, in some cases, diabetes mellitus in patients switched to DTG.

Objectives: To determine the prevalence and factors associated with hyperglycemia among PLHIV receiving DTG-based ART at Kiruddu National Referral Hospital (KNRH), Uganda.

Design: Cross-sectional study.

Methods: The study was conducted in the inpatient wards and the infectious disease outpatient clinic of KNRH from May to July 2022. Participants aged ⩾18 years on a DTG-based ART regimen for at least 3 months were consecutively enrolled and interviewed using a research assistant administered questionnaire for sociodemographic and clinical characteristics. HbA1c was measured using whole blood Architect Ci4100® (Abbott, Illinois, USA), with hyperglycemia defined using a cut-off of ⩾5.7% as per the Uganda Diabetes Association guidelines. Factors associated with hyperglycemia were examined through logistic regression, adjusting for pertinent confounders, in STATA 17. A significance level was set at $p < 0.05$.

Results: A total of 398 PLHIV with a median age of 40.5 years (IQR: 32–49) were enrolled. More than half were females (58.3%, $n = 232$) and the majority (90%) had a CD4 count above 200 cells/μL. About 16% had a family history of diabetes, 11.73% ($n = 46$) showed elevated blood pressure levels, and 16.7% ($n = 64$) had obesity. Hyperglycemia was present in 12.8% ($n = 51$), with 10.3% having pre-diabetes ($n = 41$) and 2.5% with diabetes mellitus ($n = 10$). At bivariate analysis, hyperglycemia was significantly associated with age >40 years ($p < 0.001$), herbal medicine use ($p = 0.03$), being widowed ($p < 0.001$), obesity ($p = 0.042$), hypertension ($p = 0.002$) and >3 since diagnosis with HIV ($p = 0.030$). At multivariable regression, only age >40 (AOR 2.55, 95% CI: 1.05–6.23, $p = 0.039$) and hypertension (AOR 2.93, 95% CI: 1.07–8.02, $p = 0.036$) remained significantly associated with hyperglycemia.

Conclusion: More than 1 in 10 patients on DTG-based ART in our study had hyperglycemia. We recommend regular monitoring of plasma glucose, especially for patients >40 years old and those with other comorbidities, before starting/switching to DTG regimens. Longitudinal studies are recommended to determine the underlying mechanisms of hyperglycemia in this population.

Keywords: antiretroviral therapy, dolutegravir, HIV/AIDS, hyperglycemia, Uganda

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Introduction

Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) continues to be a global health concern, with approximately 38 million people living with the virus in 2022.[1] Over the past four decades, the quality and prognosis of people living with HIV/AIDS have significantly improved, and this is primarily attributed to the widespread use of lifelong antiretroviral therapy (ART) with improved tolerability in clinical practice.[2] The ambitious 95-95-95 target by The Joint United Nations Program on HIV/AIDS (UNAIDS), which seeks to end AIDS by 2030, aims for 95% of all people living with HIV to know their status, 95% of all persons diagnosed with HIV to receive ART, and 95% of all individuals on ART to achieve viral suppression.[3] This strategy champions a "test and treat approach," advocating that individuals testing positive for HIV should be initiated on ART irrespective of their CD4 count or World Health Organization (WHO) clinical stage.[4,5]

The recently released UNAIDS 2023 update estimates that 76.4% (29.8 million) of the PLWHIV in 2022 are on ART, with countries like Botswana, Rwanda, Tanzania, Zimbabwe and Eswatini achieving the 95-95-95 target.[1] Whereas ART has been a cornerstone in the battle against HIV/AIDS, yielding significant improvements in viral suppression and patient outcomes, it's not without its complications. Efavirenz, once a mainstay in first-line treatment, has been associated with notable neuropsychiatric effects.[6] Protease inhibitors, such as Lopinavir and Ritonavir, while effective, have raised metabolic concerns, including dyslipidemia,[7] insulin resistance,[8] and, potentially, hyperglycemia.[7] More than a decade ago, a study of PLHIV in an ART clinic in urban Uganda found a prevalence of dyslipidemia and hyperglycemia of 81.5% and 16.3%, respectively.[9] Recent studies have also shown the association of some ART regimens with hyperglycemia and an increased risk of diabetes in this population.

Dolutegravir (DTG), a newer and prominent second-generation integrase strand transfer inhibitor, acts by inhibiting the HIV integrase enzyme, preventing the virus from integrating its genetic material into host DNA (Deoxyribonucleic acid) and thus halting viral replication. Recognizing its potential, the WHO recommended dolutegravir as a preferred first-line regimen for adults and adolescents in 2019. This endorsement was supported by DTG's superior potency, reduced drug resistance propensity, and overall favorable safety profile. After the WHO's recommendation, many countries, particularly those with high HIV burdens, have rapidly integrated dolutegravir into their national treatment guidelines, marking its widespread global adoption and signaling a paradigm shift in HIV therapy.

Uganda ART guidelines have recently been updated, and dolutegravir-based regimens are recommended.[10,11] However, DTG use has also been associated with an increased risk of developing hyperglycemia in several studies, and these have been associated with older age and other comorbidities like hypertension.[12–15] In a recent study by Namulindwa et al.[16] investigating the adverse side effects of DTG-based regimens in HIV-positive patients at Mbarara Regional Referral Hospital noted that the prevalence of hyperglycemia was 7.3%, and the associated factors included male sex and WHO staging. In a qualitative study by Zakumumpa et al., 2021, people living with HIV/AIDS reported hyperglycemia as the most common side effect of dolutegravir, followed by insomnia, weight gain, and reduced libido.[17] While inconclusive, it is postulated that DTG inhibits insulin secretion and signaling, partly through the chelation of magnesium.[15]

There is, however, no study among patients at Kiruddu National Referral Hospital (KNRH), Uganda's largest hospital that offers internal medicine services to the country, necessitating this study. This study aimed to determine the prevalence and factors associated with hyperglycemia among persons living with HIV receiving DTG-based ART at KNRH, Uganda.

Methods

Study design

This research used a cross-sectional study design employing quantitative techniques between May and July 2022.

Study area

The study was conducted at KNRH, a tertiary public healthcare facility in Kampala City. It has a capacity of 200 beds and 14 outpatient clinics with a population of 300–500 patients daily. The hospital's infectious disease ward predominantly

provides inpatient care to people living with HIV/AIDS. At the time of the survey, 2249 active clients were living with HIV/AIDS, enrolled in care, and on follow-up. Of these, 918 are on a DTG-based regimen, either switched or newly initiated on Highly Active Anti-retroviral Therapy (HAART) but must have been on HAART for ⩾3 months. At the time of the survey, two DTG-containing HAART regimens were being provided at the institution: Tenofovir/Lamuvidine/Dolutegravir and Abacavir/Lamuvidine/Dolutegravir.

Study population

The study population consisted of all individuals living with a confirmed diagnosis of HIV/AIDS seeking healthcare at KNRH.

Inclusion and exclusion criteria

Participants in this study were individuals diagnosed with HIV/AIDS, aged 18 or older, receiving DTG-based ART treatment for at least 3 months. They were either receiving care at the ART clinic or hospitalized at KNRH. Informed consent was obtained from all participants. However, participants with a history of diabetes mellitus before starting HAART, those with end-stage renal disease, or pregnant individuals at the time of recruitment were excluded.

Sample size calculation and sampling

The sample size for the prevalence of hyperglycemia in this population was estimated using the Kish and Leslie Formula for descriptive studies.[18]

$$N = \frac{Z^2 pq}{d^2}$$

N = sample size required
Z = standard normal value corresponding to 95% confidence interval = 1.96
P = Prevalence of hyperglycemia in HIV-positive patients receiving HAART at Jugal Hospital, Harar, Ethiopia, was 7.1%[19]
$q = 1 - p$
d = acceptable error limit = 5%

Hence, the sample size needed was:

$$N = \frac{1.96 \times 1.96 \times 0.071 \times 0.929}{0.05 \times 0.05} = 102$$

Adjusting for non-response of 10% -
$N = n/0.9 = 102/0.9 = 114$

Therefore, the sample size estimation was 114

The sample size needed to study the factors associated with hyperglycemia among patients on Dolutegravir (DTG) attending KNRH was calculated using the formula for the sample size for two proportions.

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 * \left(p_1(1-p_1) + p_2(1-p_2)\right)}{\left(p_1 - p_2\right)^2}$$

where n is the number of participants per group.
$Z_{\alpha/2} = 1.96$ is the standard normal value of z corresponding to a 5% level of confidence
$Z_{\beta} = 0.84$ is the standard normal value of z corresponding to the power of the study of 80%
P_1 and p_2 correspond to proportions with and without the factor of interest but with hyperglycemia

Using age as one of the associated factors from the literature,

$P_1 = 11.1\%$ is the proportion of participants greater or equal to 40 years of age who were on HAART and had diabetes mellitus[19]

$P_2 = 3.5\%$ is the proportion of participants less than 40 years of age who were on HAART and had diabetes mellitus[19]

$n = 179$ participants per group

Therefore, the participants were doubled for two proportions, giving 358 participants.

We adjusted for potential non-response by adding 10% to the calculated sample size, giving a final sample of 398 participants. A higher sample size of 398 participants was considered based on the sample size calculation of two proportions.

Study variables

Independent variables. The study assessed two categories of independent variables – sociodemographic and clinical factors. Sociodemographic variables included age, sex, level of education, employment status, high-fat diet intake, alcohol intake, smoking, physical activity, herbal medicine

use, and family history of DM. The clinical data collected included the medication history (HAART type and duration), WHO staging, CD4 count, viral load, adherence, co-prescribed medications, comorbid conditions associated with hyperglycemia, the body mass index, and blood pressure at assessment. Adherence was retrieved from the patient's files and defined according to the Consolidated guidelines for the prevention and treatment of HIV and AIDS in Uganda.[20]

Dependent variables. The primary outcome variable was hyperglycemia, defined by an HbA1c of 5.7% and above based on the Uganda Diabetes Association guidelines. Hyperglycemia was further subcategorized into pre-diabetes (HbA1c of 5.7%–6.4%) and diabetes (⩾6.5%) as defined by the WHO.

Study procedures. Screening for eligibility was done for patients admitted to the inpatient wards and those seen in the HIV clinic of KNRH. Informed consent was obtained from eligible patients before enrollment.

A pretested data collection tool was administered to collect demographic and clinical history.

The CD4 cell count and HIV viral load results were obtained from the patient's records (Ministry of Health HIV ART blue card). Anthropometric measurements were done while the participant was standing, which included measuring weight in kilograms using a weighing scale and height in centimeters using a stadiometer. Then, the BMI was calculated and recorded in the data collection tool. HbA1c was measured using whole blood Architect Ci4100® (Abbot, Chicago, Illinois, USA). The test results were then entered into patient-specific files. The data was then entered into a pre-designed case report form developed by the investigators and deployed into Kobo Toolbox, a web-based data entry system (https://www.kobotoolbox.org/).

The HbA1c test principle used in this study is described extensively elsewhere.[21] In summary, the Hemoglobin A1c (HbA1c) assay measures two concentrations, glycated hemoglobin (HbA1c) and total hemoglobin (THb), to calculate HbA1c as a percentage of total hemoglobin, expressed in National Glycohemoglobin Standardization Program units or International Federation of Clinical Chemistry (IFCC) units (mmol/mol). This enzymatic assay specifically targets N-terminal fructosyl dipeptides of the β-chain of HbA1c. Initially, erythrocytes are lysed, converting hemoglobin to methemoglobin via sodium nitrite. Upon adding Reagent 1, the protease cleaves the glycosylated N-terminal dipeptide (fructosyl-VH) of the β-chain. Sodium azide then converts hemoglobin to stable methemoglobin azide, with its concentration determined by absorbance measurement. Introducing Reagent 2 and fructosyl peptide oxidase initiates a reaction with fructosyl-VH, allowing HbA1c concentration measurement through the resultant hydrogen peroxide.

Quality control

Quality of laboratory performance, data collection, and procedures was managed by internal and external controls. The ARCHITECT HbA1c calibrators are aligned to IFCC reference calibrators through internal value assignment in which calibrator values must meet the sponsor's predetermined acceptance criteria within a set specification determined by the manufacturer.

The value-assigned A1c Calibrator values are within the following HbA1c ranges Calibrator 1: 4.59%–6.02% HbA1c Calibrator 2: 10.52%–13.37% HbA1c.

The HbA1c controls, low and high, are values assigned using the secondary calibrators. The values obtained must meet the sponsor's predetermined acceptance criteria. The value-assigned A1c Control values are within the following HbA1c ranges: Control L: 4.59%–6.02% HbA1c Control H: 9.42%–11.07% HbA1c.

Data analysis

The data was exported to Microsoft Excel 2016 for cleaning and coding and then to the STATA 17.0 software package (StataCorp LLC, College Station, TX, USA) for statistical analysis. Of the 448 participants in the original dataset, 50 were excluded because of ineligibility, and the final data analyzed included 398 participants. In univariate analysis, continuous numerical variables were characterized based on their distribution: for data adhering to a normal distribution, the mean and standard deviation were analyzed, while for data not following a normal distribution, the median and interquartile range were used. Categorical

variables were expressed in terms of frequencies and percentages. To identify variables associated with hyperglycemia, a bivariate analysis was conducted. For categorical variables, associations were examined using Chi-square tests or Fisher's exact test as appropriate. Bivariate logistic regression was utilized to evaluate the relationship between variables and hyperglycemia, with findings reported as crude odds ratios, accompanied by their 95% confidence intervals and *p*-values.

For the multivariate analysis, we constructed a model incorporating variables identified as potentially associated with hyperglycemia based on a review of the literature and expert consultations, along with any variable demonstrating a *p*-value below 0.2 in the bivariate analysis. The outcomes of this multivariate model were articulated through adjusted odds ratios and their 95% confidence intervals. Variables achieving a *p*-value under 0.05 were deemed statistically significant at a 95% confidence level.

Results

Characteristics of the participants

Of the 398 participants, (10.8%, 43/398) were admitted to the inpatient wards, whereas 89.2% (355/398) were outpatients. The median age of the participants was 40.5 years (interquartile range (IQR): 32–49 years), with half of the participants aged between 18 and 40 years (50%, 199/398). Females constituted more than half (58.3%, 232/398). Only 16.8% (67/398) of the participants had a family history of hyperglycemia/diabetes.

Smoking and alcohol intake were at 1.0% (4/398) and 13.6% (54/398), respectively (Table 1). While 68.8% (274/398) reported frequently being on a high-fat diet.

Table 1 summarizes the sociodemographic characteristics of the participants.

Of the 398 participants, (9.3%, 37/398) were diagnosed with hypertension whereas (10.3%, 41/398) had CD4 counts below 200 cells/μL. and more than half (54.8%, 218/398) were found to have suppressed viral loads (<1000 copies/ml). In terms of HIV progression, only a small proportion (4.5%, 14/398) had WHO stage four HIV disease. Most participants (95.5%, 380/398) had average adherence to HAART, according to Uganda's national guidelines. Only (6.3%, 25/398) of the study participants had concurrent opportunistic infections at the time of the survey, with tuberculosis accounting for (72.0%, 18/25) of such cases. Other clinical characteristics are described in Table 2 below.

Table 1. Social and demographic characteristics of the study participants.

Variable (*N* = 398)	Frequency	%
Age (years)		
18–40	199	50.0
41–60	180	45.2
>60	19	4.8
Department		
Outpatient	355	89.2
Inpatient	43	10.8
Sex		
Female	232	58.3
Male	166	41.7
Marital status		
Married	198	49.8
Separated	56	14.1
Single	119	29.9
Widowed	25	6.3
Education level		
Informal	44	11.1
Primary	172	43.2
Secondary	147	36.9
Tertiary	35	9.0
Employment status		
Employed	301	75.6
Unemployed	97	24.4
Family history of diabetes or hyperglycemia	67	16.8
Alcohol use	54	13.6
Smoking	4	1.0

Table 2. Clinical characteristics of the study participants.

Variables	Frequency	%
Blood pressure (mm Hg) ($n=392$)		
Normotensive (100–129/60–89)	175	44.6
Hypertensive ⩾ 130/90	46	11.7
Low blood pressure <100/60	171	43.6
Body mass index (kg/m^2) ($n=384$)		
<18.5	38	9.9
18.5–24.5	196	51.0
25.0–29.9	86	22.4
⩾30.0	64	16.7
Comorbidities		
Hypertension	37	9.3
Heart failure	2	0.5
Malignancy	1	0.3
CD4 count (cells/μL)		
CD4 > 200	68	17.1
CD4 < 200	41	10.3
No CD4 count	289	72.6
Viral load (copies/ml)		
Viral load >1000	8	2.0
Viral load <1000	218	54.8
No viral load done	172	43.2
Patient education & counseling for DTG Adverse Drug Effects (ADE)	128	32.2
Duration on DTG (years)		
<1 year	146	36.7
1–2 years	120	30.2
2 years	132	33.2
Reported adherence to HAART		
Good > 95%	10	2.5
Average 50%–95%	380	95.5
Poor < 50%	8	2.0
World Health Organization (WHO) stage for HIV disease		
1	326	81.9
2	35	8.8
3	19	4.8
4	18	4.5
Concurrent opportunistic infections		
No	373	93.7
Yes	25	6.3

DTG, Dolutegravir; HAART, highly active anti-retroviral therapy.

The prevalence of hyperglycemia among persons living with HIV/AIDS in this study was 12.8% (51/398). On sub-categorization, ($n=10$) were classified as diabetic, whereas (10%, 41/398) were pre-diabetic. Persons with diabetes were significantly older than those with pre-diabetes, who were, in turn, older than those with normoglycemia. At bivariate analysis, factors that were significantly associated with hyperglycemia included age: 41–60 years (crude odds ratio (COR): 4.29, 95% CI: 2.29–10.57, $p<0.001$), age >60 (COR: 15.35, 95% CI: 4.96–47.52, $p<0.001$) (Figure 1).

Herbal medicine use (COR: 2.82, 95% CI: 1.41–5.66, $p=0.003$), being widowed (COR 5.7, 95% CI: 2.32–13.98, $p<0.001$), BMI ⩾ 30 (COR: 3.89, 95% CI: 1.05–14.38, $p=0.042$), history of hypertension (COR: 3.38, 95% CI: 1.55–7.37, $p=0.002$), CD4 count <200 cells/μL (COR = 2.11, 95% CI: 0.7–6.34, $p=0.182$), high blood pressure (COR 2.35, 95% CI: 1.19–4.62, $p=0.013$), and ⩾3 years with HIV (COR: 3.39, 95% CI: 1.51–7.63, $p=0.03$) were also associated with hyperglycemia. Tables 3 and 4 summarize the bivariate analysis results.

At multivariable logistic regression (Table 5), only age above 40 years (AOR 2.55, 95% CI: 1.05–6.23, $p=0.039$) and a history of hypertension (AOR 2.93, 95% CI: 1.07–8.02, $p=0.036$) remained significantly associated with hyperglycemia.

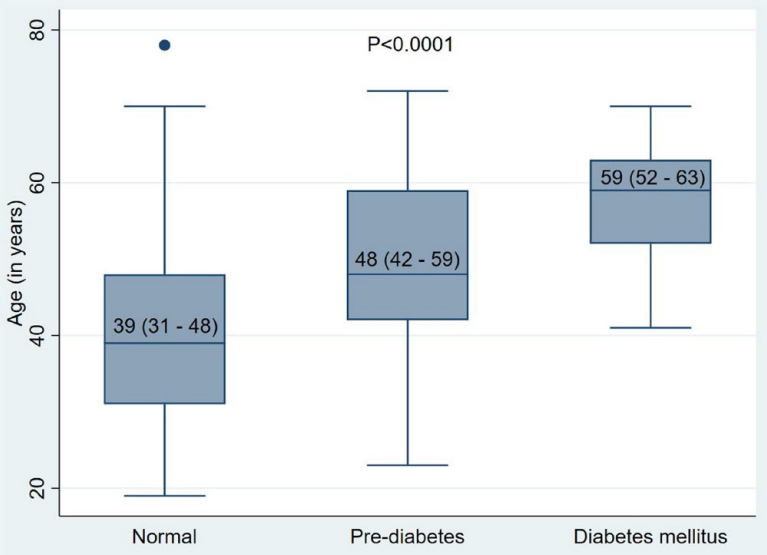

Figure 1. Distribution of glycemic status across age among people living with HIV/AIDS in Uganda.

Table 3. Bivariate analysis showing the distribution of sociodemographic factors associated with hyperglycemia among people living with HIV/AIDS on dolutegravir-based regimens.

Variable (*N* = 398)	Normoglycemia	Hyperglycemia	X^2 *p*-value	Odds ratio (95% CI)	*p*
Age (Years)					
18–40	190 (54.8)	9 (17.6)	0.000	1.00	
41–60	146 (42.1)	34 (66.7)		4.92 (2.29–10.57)	0.000
>60	11 (3.2)	8 (15.7)		15.35 (4.96–47.52)	0.000
Department					
Inpatient Department (IPD)	35 (10.1)	8 (15.7)	0.229	1.00	
Outpatient Department (OPD)	312 (89.9)	43 (84.3)		0.6 (0.26–1.39)	0.233
Sex					
Female	199 (57.3)	33 (64.7)	0.320	1.00	
Male	148 (42.7)	18 (35.3)		0.73 (0.4–1.35)	0.321
Family history of diabetes or hyperglycemia	56 (16.1)	11 (21.6)	0.333	1.43 (0.69–2.95)	0.335
Alcohol use	48 (13.8)	6 (11.8)	0.687	0.83 (0.34–2.05)	0.688
Smoking	3 (0.9)	1 (2)	0.424	2.29 (0.23–22.41)	0.478
Level of physical activity					
None	41 (11.9)	6 (11.8)	0.142	1.00	
Minimal	42 (12.2)	10 (19.6)		0.81 (0.31–2.07)	0.656

(Continued)

Table 3. (Continued)

Variable (*N* = 398)	Normoglycemia	Hyperglycemia	X^2 *p*-value	Odds ratio (95% CI)	*p*
Moderate	25 (7.2)	7 (13.7)		1.63 (0.54–4.89)	0.386
Active	237 (68.7)	28 (54.9)		1.91 (0.58–6.34)	0.289
High-fat diet	243 (70)	31 (60.8)	0.203	0.67 (0.36–1.24)	0.206
Prescribed corticosteroids, thiazides, or beta-blockers	14 (4)	4 (7.8)	0.267	2.02 (0.64–6.41)	0.230
Herbal medicine use	41 (11.8)	14 (27.5)	0.003	2.82 (1.41–5.66)	0.003

Table 4. Bivariate analysis showing the distribution and clinical factors associated with hyperglycemia among HIV-positive individuals on dolutegravir-based regimen.

Variable (*N* = 398)	Normoglycemia	Hyperglycemia	X^2 *p*-value	Odds ratio (95% CI)	*p*
Body mass index					
<18.5	35 (10.5)	3 (5.9)	0.010	1.00	
18.5–24.5	178 (53.5)	18 (35.3)		1.18 (0.33–4.22)	0.799
25.0–29.9	72 (21.6)	14 (27.5)		2.27 (0.61–8.41)	0.221
⩾30.0	48 (14.4)	16 (31.4)		3.89 (1.05–14.38)	0.042
Blood pressure					
Normal	161 (47.2)	14 (27.5)	0.030	1.00	
Low blood pressure	38 (11.1)	8 (15.7)		2.42 (0.95–6.18)	0.065
High blood pressure	142 (41.6)	29 (56.9)		2.35 (1.19–4.62)	0.013
Comorbidities					
Hypertension	26 (7.5)	11 (21.6)	0.001	3.38 (1.55–7.37)	0.002
TB	14 (4)	2 (3.9)	1.000	0.97 (0.21–4.4)	0.969
CD4 count					
CD4 > 200 cells/μL	61 (17.6)	7 (13.7)	0.356	1.00	
CD4 < 200 cells/μL	33 (9.5)	8 (15.7)		2.11 (0.7–6.34)	0.182
No CD4 count done	253 (72.9)	36 (70.6)		1.24 (0.53–2.92)	0.623
Viral load					
Viral load >1000	8 (2.3)	0 (0)	0.741	1.00	
Viral load <1000	190 (54.8)	28 (54.9)		0.95 (0.53–1.73)	0.878
No viral load done	149 (42.9)	23 (45.1)			

(Continued)

Table 4. (Continued)

Variable ($N=398$)	Normoglycemia	Hyperglycemia	X^2 p-value	Odds ratio (95% CI)	p
Duration on ART (months)					
<1 year	127 (36.6)	19 (37.3)	0.992	1.00	
1–2 years	105 (30.3)	15 (29.4)		0.95 (0.46–1.97)	0.901
>2 years	115 (33.1)	17 (33.3)		0.99 (0.49–1.99)	0.973
WHO stage					
1	285 (82.1)	41 (80.4)	0.527	1.00	
2	32 (9.2)	3 (5.9)		0.65 (0.19–2.22)	0.494
3	15 (4.3)	4 (7.8)		1.85 (0.59–5.86)	0.293
4	15 (4.3)	3 (5.9)		1.39 (0.39–5.01)	0.614
Concurrent opportunistic infections					
No	326 (93.9)	47 (92.2)	0.545	1.00	
Yes	21 (6.1)	4 (7.8)		1.32 (0.43–4.02)	0.624
Plasma glucose monitoring					
No	340 (98)	50 (98)	1.000	1.00	
Yes	7 (2)	1 (2)		0.97 (0.12–8.06)	0.979
Adherence					
Average 50%–95%	10 (2.9)	0 (0)	0.527	NA	
Good > 95%	329 (94.8)	51 (100)			
Poor < 50%	8 (2.3)	0 (0)			
Duration from diagnosis with HIV					
<5 years	156 (45)	14 (28.6)	0.020	1.00	
5–10 years	105 (30.3)	14 (28.6)		1.49 (0.68–3.24)	0.320
10–15 years	46 (13.3)	14 (28.6)		3.39 (1.51–7.63)	0.003
>15 years	37 (10.7)	7 (14.3)		2.11 (0.79–5.59)	0.134

ART, antiretroviral therapy.

Discussion

Our cross-sectional study conducted at Kiruddu National Referral Hospital revealed that the prevalence of hyperglycemia in PLWHIV in Uganda is 12.8% – that is, approximately 1 in 10 PLWHIV has hyperglycemia. About 10.3% had pre-diabetes, whereas 2.5% had diabetes mellitus. The present study indicated that people with age > 40 years had 2.5 times higher odds of developing hyperglycemia. The finding of this study showed that clients with hypertension had twice higher odds of developing hyperglycemia than non-hypertensive clients.

The current study had a higher prevalence of diabetes mellitus (3%) compared to the national

Table 5. Multivariate logistic regression showing factors associated with hyperglycemia among patients with HIV on dolutegravir-based regimen.

Variables (*N* = 398)	Adjusted Odds ratio	95% CI	*p*-value
Age in years			
<40	1.00		
40+	2.55	1.05–6.23	0.039
Gender			
Female	1.00		
Male	0.90	0.41–1.97	0.790
Unit			
Inpatient department	1.00		
Outpatient department	0.67	0.21–2.15	0.502
Marital status			
Married	1.00		
Separated	1.55	0.6–3.99	0.366
Single	0.46	0.17–1.24	0.125
Widowed	2.78	0.78–9.89	0.113
Level of education			
None	1.00		
Primary	0.67	0.24–1.88	0.446
Secondary	0.32	0.1–1.02	0.055
Tertiary	1.09	0.28–4.3	0.903
Physical activity			
None	1.00		
Minimal	2.33	0.65–8.27	0.192
Moderate	2.12	0.47–9.48	0.326
Active	0.97	0.32–2.9	0.954
Prescribed corticosteroids, thiazides, or beta-blockers	1.01	0.21–4.85	0.994
Hypertension	2.93	1.07–8.02	0.036
Family history of diabetes mellitus or hyperglycemia	1.61	0.69–3.79	0.272
CD4 count			
High > 200	1.00		
Low < 200	2.70	0.76–9.6	0.126
Not done	1.51	0.58–3.96	0.401

rates of 1.4% for diabetes mellitus and 2.1% for impaired fasting glucose.[22] In this particular national survey in 2014, approximately 48.9% of diabetes were not aware of their hyperglycemia status. The prevalence of hyperglycemia in our study was higher than in previous studies on DTG-associated hyperglycemia: 7.3% at a regional referral hospital and 0.47% at an HIV care center.[16] It is, however, lower than that reported at lower-tier Health Center IV HIV clinics (18.4%–22.6%) in Kampala, Uganda.[23,24] Studies outside Uganda have reported lower and higher findings—approximately 8% in Ethiopia[25] and 19.9% in China.[26] Variations can be attributed to differences in study populations, methodologies, local healthcare practices, awareness levels, genetic predispositions, healthcare infrastructure, dietary habits, and varying HIV and HAART management protocols across nations.

Factors that were associated with hyperglycemia at multivariable analysis included age >40 years and hypertension as a comorbidity. In our study, persons above 40 years had 2.5 odds of developing hyperglycemia, similar to another study in Uganda at an HIV care center.[12] Similar findings have also been reported from Malawi and Iran.[27,28] Altered glucose metabolism and insulin resistance increase with age, resulting in an increased risk of developing hyperglycemia and other comorbidities like hypertension in PLHIV.[29] Previous studies also show that as PLHIV lives longer while on HAART, the risk of insulin resistance increases.[30]

In our study, PLHIV with hypertension were nearly three times more likely to have hyperglycemia. This is similar to previous findings in the United States and Ethiopia.[19,31–33] Hypertension may be a related comorbidity of diabetes, as frequently seen in metabolic syndrome.[34–38] The clinical implication of this is that the selection of antihypertensive therapy in PLHIV needs to be careful to mitigate the risk of exacerbating hyperglycemia, especially in individuals with or at risk of developing diabetes.

The findings from this study bear several significant implications. Given the high prevalence of hyperglycemia among PLHIV, especially those on DTG-based ART, clinicians need to incorporate routine blood glucose monitoring for early detection and timely management. This is crucial as hyperglycemia can have dire consequences if not detected early and managed appropriately. With almost half the participants lacking baseline blood glucose measurements, health policies need to prioritize glucose monitoring as a standard part of HIV care, given the widespread use of DTG-based regimens. Additionally, training programs for health workers must underscore the potential link between dolutegravir and diabetes, enhancing awareness and improving patient management.

The inconsistent findings across various studies concerning factors like gender and CD4 count association with hyperglycemia highlight the need for more research. These studies, preferably longitudinal, should delve deeper into the complex interplay of genetic, metabolic, and environmental factors that might influence hyperglycemia among PLHIV. Additionally, the mechanisms by which ART, especially dolutegravir, may induce or exacerbate hyperglycemia need further exploration, which can potentially inform better drug development in the future.

Our study is not without limitations. Firstly, its cross-sectional design restricts our ability to deduce causality or establish the trends in hyperglycemia over time in PLWHIV. Furthermore, the study was conducted at a single national referral hospital, limiting generalizability. Participant self-reporting raises the possibility of recall bias. Hemoglobin levels were not evaluated, hence limiting our interpretation of HbA1c measurements and the questions used in the questionnaire used in the study were not validated.

Conclusion

In this study, 12.8% of PLHIV taking DTG-based ART experienced hyperglycemia. We recommend regularly monitoring the plasma glucose levels of PLHIV on ART regimens, including DTG. Additionally, it is recommended that longitudinal studies be conducted to determine the underlying mechanisms of the problem.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Makerere University School of Medicine Research Ethics Committee (Mak-SOMREC-2022-298). All participants provided written informed consent prior to enrollment into this study.

Consent for publication
Not applicable.

Author contributions
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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The minimal dataset is available within the paper. Additional data is available upon reasonable requests from the corresponding author (Dr Lillian Happy Byereta) at hbyereta@gmail.com.

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