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Incidence of type 2 diabetes mellitus in persons living with HIV initiated on dolutegravir-based antiretroviral regimen in Ghana: an observational longitudinal study

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Abstract

Background Few studies have reported hyperglycemia and diabetic ketoacidosis in patients on dolutegravir (DTG) treatment. This study determined the effect of DTG on fasting blood glucose levels in a cohort of persons living with HIV (PLHIV) in Ghana and initiating DTG regimens.

Methods A two-year observational longitudinal cohort study conducted from 12th October 2020 to 31st December 2022. Fasting blood glucose was measured at baseline, 12, 24, 36 and 72 weeks for patients after a 12 h overnight fast. The Kaplan-Meier estimator was used to estimate the risk of developing type 2 diabetes mellitus (T2DM). Cox proportional hazard model was used in estimating hazard ratios.

Results A total of 1334 non-diabetic patients were enrolled with 78% (1039) females and 83% (1104) were antiretroviral therapy experienced. The incidence proportion and rate of T2DM at 72 weeks were 11.8% (95%CI: 10.2–13.7) and 98.1 cases per 1000 PY (95%CI: 83.9-114.6) respectively. The median time to development of T2DM was 24 weeks post DTG initiation. Male sex (aHR 2.9 [95%CI: 1.9–4.3]), abnormal waist-hip ratio (1.67 [95% CI: 1.15–2.43]) and abnormal total serum cholesterol (aHR 1.6 [95%CI: 1.1–2.3]) were found to be significant determinants of T2DM.

Conclusion Incidence of T2DM is high among non-diabetic PLHIV within 72 weeks of initiating DTG based therapy with males having a higher risk. Longitudinal changes in waist-hip ratio and serum cholesterol among patients initiated on DTG needs to be monitored regularly.

Keywords Dolutegravir, Type 2 diabetes mellitus, Sub-Saharan Africa, ART, Cohort studies

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Background

An estimated 39 million people were living with the disease as at the end of 2022 [1]. Sub-Saharan Africa remains the most HIV-affected region, home to about 68% of the world's population of people living with HIV [2]. The UNAIDS reported that for the year 2022, 86% of all persons living with HIV (PLHIV) knew their status, 76% were accessing antiretroviral therapy (ART) and 71% were virally suppressed [1]. The significant improvement and advancement to ART have considerably improved the health and life expectancy of PLHIV [3, 4].

As a result, PLHIV are experiencing an increase in non-communicable diseases (NCDs) like cardiovascular disease and diabetes; with incidence of the latter being affected by age, as well as HIV-related factors [5–7].

The combination of nucleoside and non-nucleoside reverse transcriptase inhibitors were once preferred for first line ART, but studies show it is bedeviled with toxicities, resistance, and poor suppression [8–10]. Integrase strand transfer inhibitors (INSTIs) have been shown to have improved viral suppression, less resistance and toxicity [11].

As a result, in 2018, the World Health Organization (WHO) recommended the use of DTG as the preferred first line treatment for PLHIV, leading to many countries including Ghana, changing their ART policies without additional studies [12, 13]. However, there have been conflicting reports on the adverse effects of DTG among the PLHIV since its implementation. Key among these is the issue of hyperglycemia [14–17]. Namara et al. reported 30-times greater odds of developing hyperglycemia after initiation on INSTI-based ART regimen in a case-control study [16] whilst Mulindwa et al. also reported an incidence of 4 cases per 1000 person years after a 12 month follow up study of PLHIV initiated on INSTI-based regimen (DTG) [15]. However, a systematic review by Mulindwa et al. reported INSTI-based ART was associated with a lower risk of DM from 13 studies analyzed compared to other ART regimen [18–20, 28].

This study therefore sought to determine the incidence of diabetes and prediabetes among patients initiated on DTG based regimen in Ghana.

Methods

Study design and setting

This study is a part of a larger prospective multi-center observational cohort study conducted from 12th October 2020 to 31st December 2022 among persons living with HIV (PLHIV) in Ghana. The recruitment period was from 12th October 2020 to 31st May 2021. Patients were recruited from five ART facilities providing services at the district and tertiary levels of care: Korle Bu Teaching Hospital (KBTH), Atua Government Hospital, Kumasi South Hospital, St Martins Hospital and Kwesimintsim Hospital in Ghana.

Study participants

The study involved stable ART-naïve and experienced PLHIV patients aged 18+without the opportunistic infections and without the outcome of interest who started a DTG-based regimen, excluding those who were acutely ill, did not intend to engage with the clinic for at least 2 years, or pregnant. The dosage of DTG in the DTG-based regimen was 50 mg for each of the study participants.

Participants screening and enrollment

Out of 3682 patients screened, 0.6% (21/3682) were excluded because they were pregnant. Of the remaining 3661, 63.6% (2327/3661) had fasting blood glucose (FBG) levels in the prediabetes and type 2 diabetes range and were also excluded from the study. The remaining 1334 with normal FBG levels were enrolled into the study and followed up (Fig. 1).

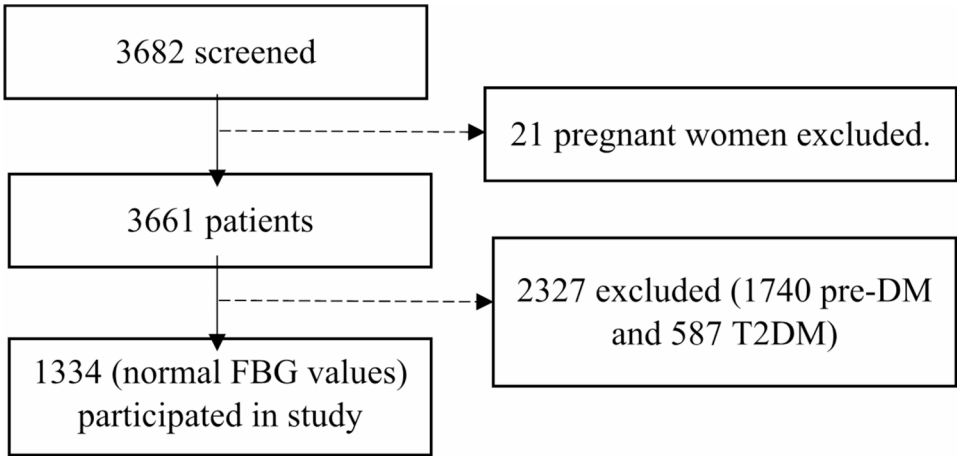

Fig. 1 Flow chart of study participants screening and enrollment into the study

Study procedure

All eligible participants identified at the clinic were approached and those who consented were enrolled. The FBG was measured with OneTouch® SelectSimple™ glucometers from Lifescan Incorporated [21, 22]. Capillary blood from the tip of the finger after an overnight fast using a lancet and the FBG measured with the glucometer. A questionnaire was then administered which collected data on socio-demographic characteristics, antiretroviral medication types, medication adherence and gynecological history (mainly the last menstrual period (LMP)) for the possibility of pregnancy and DTG reported side effects.

Clinical assessments then followed with anthropometric measurements like weight (kilograms), height (meters), waist and hip circumference (centimeters) and blood pressure (BP) (mmHg) measurements. Venous blood was then drawn from the antecubital fossa for assessment of serum lipid profile, blood urea, electrolytes and serum creatinine, alanine transaminases and C-reactive protein (CRP). Each study participant was followed up for 72 weeks (18 months). The same data was collected at baseline,12, 24, 48 and 72 weeks of follow up. When a patient misses a scheduled follow-up appointment but remains on the antiretroviral medication, the patient is still included in the study and followed-up at the next scheduled clinic visit. Patients who missed their scheduled follow-up appointment and had also stopped antiretroviral medications for a minimum of 2 weeks were censored. Each person contributed person-time years from DTG-based ART initiation until a censoring event.

Censoring event comprised of DTG discontinuation, loss to follow up, pregnancy, death, or end of study. Participants with confirmed pregnancies were censored at the time of confirmation.

ART regimen

Both ART naïve and experienced participants were given DTG based regimen (DTG in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir (TDF), lamivudine (3TC) or emtricitabine (FTC) and abacavir (ABC)).

Operational definitions

Type 2 diabetes Mellitus Any individual with fasting blood glucose≥7.0 mmol/l (126 mg/dL) [23].

Prediabetes Any individual with fasting blood glucose≥5.6 mmol/l (100 mg/dL) to 6.9 mmol/l (125 mg/dl) [23].

ART Naïve PLHIV who had no history of ART use prior to the initiation of DTG-based ART.

ART experienced PLHIV with evidence of a history of being on non-DTG containing ART prior to the initiation of dolutegravir-based ART.

At risk population The patients who do not have the outcome of interest and initiated on DTG-based regimen.

Failures Patients who develop the outcome of interest (i.e., T2DM) during follow-up in the study.

Data management and statistical analysis

Data was collected electronically by trained research assistants using the Kobo Collect toolbox software and downloaded into Microsoft Excel. Data was cleaned and checked for consistency by the study monitoring team. Data was then exported to STATA version 17 for statistical analysis.

The prevalence of T2DM was estimated as the number of people with T2DM divided by the total number of people screened at the start of the study. The primary outcome was the incidence of T2DM. This was defined as fasting blood glucose≥7.0 mmol/l (126 mg/dL) [23]. Fasting blood glucose data was categorized into "T2DM" and "no T2DM". Incidence rate of T2DM was estimated by dividing the total number of new cases identified within the follow-up period by the total person-years at risk. The Kaplan-Meier estimator was used to compute the risk of developing T2DM. The log-rank test was used to compare the survival function of developing T2DM across the various background characteristics. The Nelson-Aalen cumulative hazard function was reported for each study time point. Cox proportional hazard model with robust standard errors was used in estimating the hazard ratio. Significance level was set at 0.05.

All participants who were either lost to follow-up or ended the study without developing T2DM were censored. Any missing FBG data in between the person-time contributed to the study was assumed to be "no T2DM". Forty-seven out of 158 events in the 1334 observations had interval censoring. Four additional models were fitted in addition to the Standard Cox proportional hazard model with robust standard error ignoring the interval censoring. Poisson model with robust standard error and exposure time ignoring the interval censoring gave similar findings as the Standard Cox proportional hazard model. In accounting for interval-censoring, two approaches were used, (1) using the midpoint time for interval censored data as the time the event occurred and (2) fitting Parametric models for interval-censored survival-time data. The results from the Standard Cox proportional hazard model using midpoint time of interval-censored data with robust standard error, Poisson model with robust standard error and exposure time using midpoint time of interval-censored data,

Parametric models for interval-censored survival-time data with exponential distribution link and robust standard error were all similar to results from the Standard Cox proportional hazard model with robust standard error ignoring the interval censoring.

Quality assurance

Interviewers were trained on use of electronic tables and data collection software. We measured and recorded participants' BP using an automatic Omron HEM 7124 machine, height using Secca 285 wireless stadiometer and weight using PICOOC smart electronic scale. These instruments were calibrated by the biomedical engineering department of KBTH prior to use. Patients sat in a straight back chair with back supported and their feet on floor for 15 min [24]. The patient's arm was supported and the middle of the Omron cuff was positioned on patient's upper arm at the level of the right atrium (midpoint of the sternum) before an average of two BPs were measured [24]. Trained personnel were involved in blood draws, documentation, storage, and transport to ISO accredited laboratory (ISO 15189:2012).

Results

Baseline demographic and clinical characteristics

Of 1334 patients enrolled, 78% (1039) were female. Most (64% (852/1334)) were aged 25–49 years and 37% (492/1334) were married (Table 1).

Eighty three percent (1104/1334) were ART experienced and of these, 48.6% (536/1104) were on ART for <5 years (Table 1). Most [48% (643/1334)] patients had normal BMI at time of enrollment and 56% (741/1324) had normal waist-to-hip ratio. 43% of participants had normal BP measurements levels at enrollment.

Incidence proportion and rate of T2DM

The average fasting blood sugar level of study participants at baseline was 5.1 ± 0.4 mmol/l. The maximum follow-up time was 72 weeks. Total person years (PY) contributed was 1611.25 with an incidence proportion of 11.8% (95% CI: 10.2–13.7) (Table 2). The overall incidence rate was 98.1 cases per 1000 PY (95% CI: 83.9-114.6).

The incidence rate of T2DM among patients with normal weight was 88.9 (95% CI: 70.2–112.5) cases per 1000 PY whilst that for obese was 119.7 (95% CI: 87.1–164.5) cases per 1000 PY (Table 2).

The incidence proportion and rate of T2DM among patients with hypertension was 14.7% (95% CI: 11.4–18.7) and 119.0 (95% CI: 91.2–155.4) cases per 1000 PY respectively (Table 2).

Survival function estimation

The median time to development of T2DM was 24 weeks after DTG initiation. Males had a higher probability of

Table 1 Characteristics of persons living with HIV initiated on dolutegravir based regimen in Ghana, 2020–2022

Characteristic	Frequency	Percentage
Age (years)		
<25	53	3.97
25–49	852	63.87
50–59	277	20.76
>60	152	11.39
Sex		
Male	295	22.11
Female	1039	77.89
Marital Status		
Never Married	287	21.51
Currently Married/cohabiting	586	43.93
Previously Married	461	34.56
Occupational status		
Not employed	252	18.89
Employed	1052	78.86
Student	30	2.25
Type of HIV		
HIV-1	1287	96.48
HIV-2	12	0.9
HIV1/HIV2	35	2.62
Treatment classification		
ART naive	170	12.74
ART experienced	1164	87.26
Duration of HIV diagnosis (years)		
<5	667	50.68
5–10	370	28.12
>10	279	21.2
Duration on ART (years) (*n* = 1104)		
<5	536	48.55
5–10	366	33.15
>10	202	18.3
Comorbidity*		
No	1167	87.48
Yes	167	12.52
Body Mass Index (BMI) (kg/m^2)		
Under-weight (< 18.5)	119	8.92
Normal (18.5–24.9)	643	48.2
Overweight (25-29.9)	322	24.14
Obesity (≥ 30)	250	18.74
Waist-to-Hip ratio		
Normal (Male ≤ 0.9; Female ≤ 0.85)	741	55.97
Abnormal (Male > 0.9; Female > 0.85)	583	44.03
Blood pressure (mm/Hg)		
Normal (≤ 120/80)	574	43.03
Pre-hypertension (> 120–139/81–89)	392	29.39
Hypertension (≥ 140/90)	368	27.59
Serum Urea (mmol/L)		
Normal (2.1–7.1)	1201	90.03
Abnormal (> 7.1)	133	9.97
Serum Cholesterol (mmol/L)		
Normal (< 5.2)	968	72.56
Abnormal (≥5.2)	366	27.44

Table 1 (continued)

Characteristic	Frequency	Percentage
LDL Cholesterol (mmol/L)		
Normal (< 3.0)	657	59.35
Abnormal (≥3.0)	450	40.65
HDL Cholesterol (mmol/L)		
Normal (Male > 1.45; Female > 1.68)	385	28.86
Abnormal (Male ≤1.45; Female ≤1.68)	949	71.14
Triglycerides (mmol/L)		
Normal (< 1.7)	1126	91.84
Abnormal (≥1.7)	100	8.16
Serum Creatinine (umol/L)		
Normal (Male 62–106; Female 44–80)	1142	85.61
Abnormal (> 80)	192	14.39
C-reactive protein (CRP) (mg/L)		
Normal (< 5.0)	973	73.99
Abnormal (≥5.0)	342	26.01

HIV: Human Immunodeficiency Virus, ART: Antiretroviral Therapy; Comorbidity: Hypertension, Asthma, Tuberculosis, stroke, Kidney disease

developing T2DM compared to females (P=<0.001) whilst participants aged≥50 years had a higher probability of developing T2DM compared to those aged<50 years (P=0.002) (Fig. 2).

Determinants of T2DM

Male sex (aHR: 2.9 [95% CI: 1.9–4.3]), abnormal waist-hip ratio (aHR:1.67 [95% CI: 1.15–2.43]) and abnormal total serum cholesterol (aHR: 1.6 [95% CI: 1.1–2.3]) were significant determinants of T2DM (Table 3).

Discussion

This study assessed incidence of T2DM among Ghanaian cohorts living with HIV initiated on a DTG based antiretroviral therapy. The incidence proportion and rate of T2DM was 11.8% and 98.1 cases per 1000 PY respectively. Male participants and those aged≥50 years had a higher risk of developing T2DM compared to being female and aged<50 years respectively. Being male, having abnormal waist-hip ratio and abnormal total serum cholesterol were significant determinants of T2DM.

Our study revealed a T2DM incidence proportion of 11.8% with a median time to development of 24 weeks after initiation onto DTG. This is similar to findings from O'Halloran et al. which reported use of INSTI to be associated with 31% increased risk of new-onset hyperglycemia within 24 weeks of follow up [25]. In another study in Uganda, patients on DTG based regimen had seven times greater odds of developing diabetes compared to DTG naïve patients [14]. Similar findings of T2DM and its association with DTG have been reported in some studies in sub-Saharan Africa [16, 26, 27]. The first 24 weeks post DTG initiation for hyperglycemia is important in monitoring of patients for early interventions to avert progression to T2DM. Though the underlying mechanism for DTG associated hyperglycemia in our patients is unknown, their glycemic status was established at baseline as having normal fasting glucose levels. Thus, DTG may likely have a role to play and further studies are needed in this area to investigate genetic polymorphisms and role of DTG in influencing glucose metabolism.

However, contrary to our study findings, a systematic review of ten articles with a total of 62,400 participants on INSTI and risk of development of T2DM with follow up periods varying from one year to eighteen years, reported there was no statistically significant difference in T2DM among PLHIV on INSTIs compared to those treated with protease-inhibitors (PI) [17]. The review also reported a lower incidence of T2DM in PLHIV on INSTIs compared to those using non-nucleoside reverse transcriptase inhibitors (NNRTIs) [17]. Another systematic review of thirteen articles by Mulindwa et al. with a patient population of 72,404, reported a lower risk of T2DM compared with NNRTIs although not statistically significant [28]. The risk was however similar to those on protease inhibitor-based therapy but increased in the African population [28]. The difference in finding may be due to different geographical context as only 3 out of the 23 articles were from Africa (Uganda, Cameroon, and South Africa). Also, the study designs employed in the articles from Cameroon and South Africa were both randomized control trials whilst that from Uganda was a case-control [28]. Our study was a prospective one in a real-world setting, and this could account for the current findings being reported. The difference in geographical setting and genotypic characteristics of PLHIV will need further studies to evaluate if these differences play a major role in risk of developing T2DM. However, the increased incidence proportion of T2DM among our study participants corroborates with increased risk of T2DM in African population reported by Mulindwa et al. [28].

In this study, the incidence proportion and rate of T2DM was higher (12.6% and 101.4 per 1000PY) among ART experienced compared to 6.5% and 68 per 1000PY among ART-naïve patients. The association between being ART experienced and risk of developing T2DM was however, not statistically significant. This is in contrast to several studies including the Multicenter AIDS Cohort Study, VIKING-3 study, SPRING-2 and SINGLE studies [14, 29–33] which found that patients who were ART experienced have an increased risk of developing T2DM. This could be due to the fact that patients who have been on ART for long were probably exposed to agents from the first-generation ART, which are known to have notable metabolic toxicities resulting in insulin resistance [34]. Another study in South Africa reported increase in odds by more than three-folds of developing

Table 2 Diabetes cumulative incident proportion and rate among PLHIV on dolutegravir based regimen in Ghana, 2020–2022

	At risk	Failures	Person-years	% [95% CI]	IR per 1000PY [95%CI]
Overall	**1334**	**158**	**1611.25**	**11.84 [10.21–3.69]**	**98.06 [83.90–114.61]**
Age (years)					
18–49	905	88	1083.25	9.72 [7.96–11.83]	81.24 [65.92–100.11]
≥50	429	70	528.00	16.32 [13.11–0.12]	132.58[104.89-167.57]
Sex					
Male	295	51	333.00	17.29 [13.38–2.04]	153.15[116.39–01.52]
Female	1039	107	1278.25	10.30 [8.59–12.30]	83.71 [69.26–101.17]
Treatment classification					
ART naive	170	11	161.75	6.47 [3.62–11.31]	68.01 [37.66–122.80]
ART experienced	1164	147	1449.50	12.63[10.84 14.67]	101.41 [86.28–19.21]
Type of HIV					
HIV-1	1287	148	1549.75	11.50 [9.87–13.36]	95.50 [81.29–112.19]
HIV-2	12	2	15.75	16.67 [4.19–47.75]	126.98 [31.76 -507.74]
HIV1/HIV2	35	8	45.75	22.86 [11.86–9.49]	174.86 [87.45 -349.66]
Duration on ART					
<5 years	536	67	643.00	12.50 [9.96–15.58]	104.20 [82.01- 132.39]
5–10 years	366	39	483.25	10.66 [7.88–14.26]	80.70 [58.96–110.46]
>10 years	202	34	248.25	16.83[12.28–22.64]	136.96 [97.86- 191.68]
Duration of HIV diagnosis					
<5 years	667	70	757.75	10.49 [8.38–13.06]	92.38 [73.09–116.76]
5–10 years	370	42	485.75	11.35 [8.50–15.01]	86.46 [63.90–117.00]
>10 years	279	44	342.75	15.77[11.95–20.54]	128.37[95.53–172.50]
Comorbidity					
No	1167	130	1408.50	11.14 [9.46–13.08]	92.30 [77.72–109.61]
Yes	167	28	202.75	16.77 [11.83–3.22]	138.10 [95.35- 200.01]
Body Mass Index (BMI)kg/m^2					
Under-weight (< 18.5)	119	12	119.25	10.08 [5.81–16.93]	100.63 [57.15–77.19]
Normal (18.5–24.9)	643	69	776.25	10.73 [8.56–13.37]	88.89 [70.21–112.54]
Overweight (25–29.9)	322	39	398.25	12.11 [8.97–16.15]	97.93 [71.55–134.03]
Obesity (≥ 30)	250	38	317.50	15.20[11.26–20.21]	119.69 [87.09–64.48]
Waist-to-Hip ratio					
Normal	741	75	899.75	10.12[8.15–12.51]	83.36 [66.47–104.53]
Abnormal	583	82	701.75	14.07[11.47–17.13]	116.85[94.11–145.09]
Blood pressure (mm/Hg)					
Normal (≤ 120/80)	574	54	678.75	9.41 [7.27–12.09]	79.56 [60.93–103.88]
Pre-HPTN (> 120–139/81–89)	392	50	478.75	12.76[9.80–16.44]	104.44[79.16–137.80]
HPTN (≥ 140/90)	368	54	453.75	14.67[11.41–18.67]	119.01[91.15–155.39]
Serum Cholesterol					
Normal (< 5.2)	968	92	1172.00	9.50 [7.81–11.52]	78.50 [63.99–96.30]
Abnormal (≥5.2)	366	66	439.25	18.03[14.42–22.31]	150.26[118.05-191.25]
HDL Cholesterol					
Normal (Male > 1.45; Female > 1.68)	385	63	489.75	16.36[12.99–20.41]	128.64[100.49-164.67]
Abnormal (Male ≤1.45; Female ≤1.68)	949	95	1121.50	10.01[8.25–12.09]	84.71 [69.28–103.58]

%: Cumulative incident proportion, IR: Cumulative incident rate, CI: Confidence Interval, HIV: Human Immunodeficiency Virus, ART: Antiretroviral Therapy, PY: Person years; HPTN: hypertension

T2DM in ART experienced patients compared to ART naïve [18]. Another cohort study among 243 ART-naïve patients all receiving DTG from Uganda also reported a low incidence (4 cases per 1000 PY (1/243)) of T2DM although their sample size was small [14]. This buttress reports of increased risk of T2DM in ART experienced compared to ART-naïve patients. Therefore, it is important for clinicians to assess ART-experienced patients for risk factors for T2DM and keenly monitor them regularly for hyperglycemia as part of the clinical package when transitioned to DTG.

Being male was significantly associated with T2DM in our study and had about 3 times increased risk of developing T2DM compared to females. This was similar

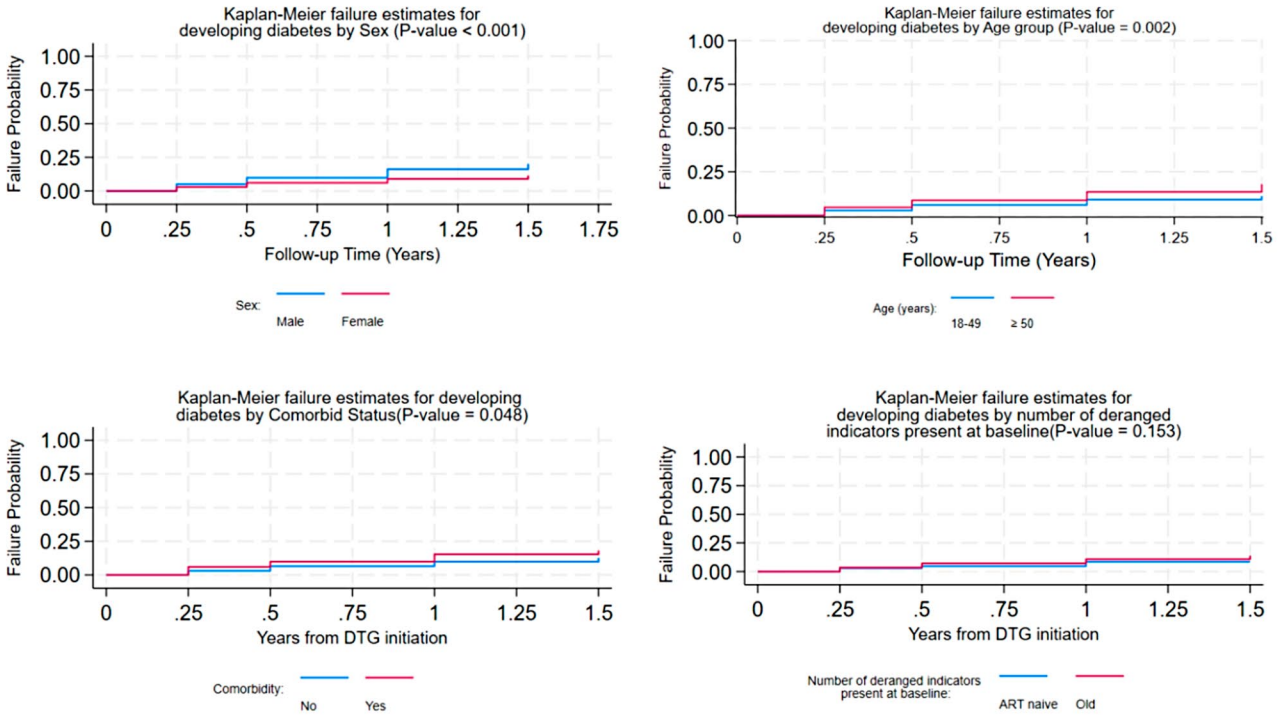

Fig. 2 Time to development of Type 2 Diabetes Mellitus among PLHIV initiated on dolutegravir based regimen in Ghana, 2020–2022

to reports by Lamorde et al. in Uganda where 81.3% of patients with DTG-associated hyperglycemia were males [35]. However, this was subject to confounding as majority of the study participants were males. Contrary to these findings, another study in Uganda did not find any association between males on DTG and risk of T2DM [16].

Our study also showed that patients aged ≥ 50 years had a 64% increased risk of developing T2DM. This is similar to findings from a Ugandan study where patients on DTG based regimen aged ≥ 56 years had twelve times the odds of developing hyperglycemia compared to those aged 18–35. Older age is one of the traditional risk factors for T2DM. Age-related impairment of pancreatic islet function and increasing insulin resistance collectively increase the risk of T2DM among older patients [36]. Older patients at high risk of T2DM should be considered for alternate regimen rather than DTG-based regimen to reduce risk of T2DM or be subject to more rigorous monitoring for early detection and institution of interventions.

In our study, the incidence of T2DM was higher among patients with elevated total cholesterol compared to those with normal levels of total cholesterol. Elevated total serum cholesterol was associated with 61% increased risk of developing T2DM in this study. Studies evaluating DTG use and lipids have reported no significant changes seen in the lipids including total cholesterol [37, 38]. Patients on efavirenz who switched to DTG were found to have reductions in lipids [38]. Though published reports indicate DTG may be of great benefit to patients with a high risk of cardiovascular disease due to lipid reduction, this needs careful interpretation as patients with elevated lipids are at risk of hyperglycemia.

Our study showed that over 60% of our study participants had high levels of pre-DM and T2DM during the screening phase which had not been earlier diagnosed. Though HIV and ART are contributing factors to NCDs among PLHIV [6, 7, 9, 10], the reasons for these high levels of pre-DM and T2DM are unclear. These participants were excluded from the study however this raises the issue of further research into the aetiopathogenesis of DM and especially in PLHIV. Genotypic and phenotypic factors may play a significant role in the development of hyperglycemia and even idiosyncratic drug reactions may be considered. More rigorous mechanistic studies need to be conducted among PLHIV to provide useful physiological insights into T2DM in PLHIV and ART.

There is a need for the development and implementation of a systematic screening plan for hyperglycemia using point of care devices in patients initiating DTG based regimen [26]. This can lead to early detection in patients with risk factors for T2DM and alternate regimen considered for patients assessed to be at high risk for T2DM [16].

Our study had limitations. Some of these include the design being observational and could possibly be exposed to bias or confounding introduced by patient

Table 3 Determinants of time to develop type 2 diabetes mellitus among PLHIV initiated on dolutegravir based regimen in Ghana, 2020–2022

	Unadjusted model		Adjusted model	
	uHR [95% CI]	***P*-value**	**aHR [95% CI]**	***P*-value**
Age				
18–49	1.00		1.00	
>=50	1.64 [1.20–2.22]	0.002	1.08 [0.74–1.58]	0.675
Sex				
Male	1.80 [1.30–2.50]	< 0.001	2.88 [1.91–4.34]	< 0.001
Female	1.00		1.00	
ART status				
ART naive	1.00		1.00	
ART Experienced	1.55 [0.84–2.84]	0.16	1.35 [0.68–2.69]	0.386
HIV type				
HIV-1	0.54 [0.28–1.04]	0.066	0.65 [0.35–1.22]	0.181
HIV-2	0.74 [0.16–3.46]	0.698	1.09 [0.23–5.13]	0.916
HIV1/HIV2	1.00		1.00	
Duration of HIV diagnosis				
< 5 years	1.00		1.00	
5–10 years	0.96 [0.66–1.40]	0.831	0.78 [0.48–1.27]	0.317
> 10 years	1.41 [0.97–2.04]	0.069	1.16 [0.56–2.39]	0.684
Mean duration on ART	1.04 [1.00–1.07]	0.057	0.99 [0.92–1.07]	0.829
Comorbidity				
No	1.00		1.00	
Yes	1.49 [1.00–2.23]	0.05	1.03 [0.64–1.64]	0.909
Body Mass Index				
Under-weight	1.09 [0.60–2.00]	0.773	0.99 [0.51–1.97]	0.995
Normal	1.00		1.00	
Overweight	1.11 [0.75–1.64]	0.600	1.04 [0.68–1.59]	0.908
Obesity	1.35 [0.92–1.99]	0.122	1.42 [0.96–2.12]	0.082
Waist-Hip ratio				
Normal	1.00		1.00	
Abnormal	1.40 [1.03–1.90]	0.033	1.67 [1.15–2.43]	0.007
Blood Pressure				
Normal	1.00		1.00	
Prehypertension	1.32 [0.91–1.93]	0.148	1.14 [0.76–1.71]	0.523
Hypertension	1.51 [1.04–2.18]	0.03	1.16 [0.76–1.78]	0.48
Total Serum Cholesterol				
Normal	1.00		1.00	
Abnormal	1.91 [1.40–2.61]	< 0.001	1.61 [1.12–2.32]	0.011
HDL Cholesterol				
Normal	1.00		1.00	
Abnormal	0.65 [0.48–0.89]	0.007	0.82 [0.57–1.16]	0.265

uHR: Unadjusted hazard ratio, aHR: Adjusted hazard ratio, CI: Confidence interval, HIV: Human Immunodeficiency Virus, ART: Antiretroviral Therapy

self-reporting. We however cross-referenced information they provided from patient records to reduce the risk of bias. Again, family history of diabetes, dietary and lifestyle characteristics of patients were not assessed though they have an impact of the outcome of interest. The study determined fasting blood sugar level by assessing capillary blood using glucometers and did not assess plasma glucose. We tried to reduce the risk by using the same brand of glucometer across all sites. In addition, the point of care tests would be easier to implement if these findings are to be translated into practice. We also did not test for Hemoglobin A1c (HbA1c) levels as part of confirmation of T2DM which would have provided a comprehensive assessment of glycemic control over time. In our general population, we do not routinely use HBA1c for diagnosis of T2DM and the same was done in this observational cohort. Detections in blood sugar fluctuations would have been more robust if patients' capacity were enhanced to frequently self-monitor, record and report blood sugar levels in-between study visits.

In spite of the limitations, the study was performed on a large representative population in Ghana, West Africa, adding on to diversity of knowledge on DTG and hyperglycemia within sub-Saharan Africa. The longitudinal nature and having an established baseline glycemic levels adds to the robustness of the study findings.

Conclusion

The incidence of T2DM among the cohort of PLHIV on DTG regime was almost 10% with a median time to development of 24 weeks after initiation onto DTG. Males and those with increased serum cholesterol were at a higher risk of developing diabetes. Screening of clients' blood glucose levels before initiation of DTG and regular monitoring of blood glucose is recommended. Further studies to investigate and conclude on the role of DTG in glucose metabolism are recommended.

Abbreviations

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral Therapy
BMI	Body Mass Index
BP	Blood Pressure
CRP	C-reactive Protein
DM	Diabetes Mellitus
DTG	Dolutegravir
FBG	Fasting Blood Sugar
FTC	Emtricitabine
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
HBA1c	Hemoglobin A1c
INSTI	Integrase Strand Transfer Inhibitor
KBTH	Korle Bu Teaching Hospital
LMP	Last Menstrual Period
NACP	The Ghana National AIDS/STI Control Programme
NCD	Non-Communicable disease
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
PI	Protease Inhibitors
PLHIV	Persons living with HIV
T2DM	Type 2 Diabetes Mellitus
TDF	Tenofovir
UNAIDs	The Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

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Author contributions

ML, EK, VG, KT, SAA contributed to study conception, design, manuscript preparation and final review. ML, EK, VG, KT, KA, PT, contributed to participant enrolment, data collection, data management, analysis and interpretation and final manuscript review. DB, MA contributed to analysis and interpretation, draft review, and final manuscript review.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due the regulations of the KBTH Ethics Committee and IRB regulations but are available from the corresponding author (Dr Vincent Ganu, vincentjganu@gmail.com) on reasonable request.

Declarations

Ethical approval and consent to participate

Approval was granted by Institutional Review Board of University of Ghana College of Health Sciences (CHS:00006220), Korle Bu Teaching Hospital (KBTH-IRB/000136/2020 and Ghana Health Service (GHS-ERC 010/08/20). Written informed consent was obtained from study participants and data confidentiality was ensured.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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