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Metabolic syndrome among a Ghanaian cohort living with HIV initiated on dolutegravir in a real-world setting: a prospective study

Kwasi Torpey,[1] Vincent Ganu ,[2] Ernest Kenu,[3] Stephen Ayisi Addo,[4] Kofi Agyabeng,[5] Magdalene Akos Odikro,[3] Raphael Adu-Gyamfi,[4] Abdul Gafaru Mohammed,[6] Margaret Lartey[2,7]

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KT, VG and ML contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Dr Vincent Ganu;
vincentjganu@gmail.com

ABSTRACT

Objectives The use of antiretroviral therapy has been linked to the development of some components of metabolic syndrome (MetS), specifically glucose intolerance, weight gain and defective lipid metabolism. This study determined the relationship between dolutegravir (DTG) and MetS in a cohort of persons living with HIV (PWH) initiating DTG-based regimen in Ghana.

Design A 2-year observational prospective study was conducted from September 2020 to August 2022.

Setting Five HIV high-burden facilities providing antiretroviral therapy services at the district and tertiary levels of care in Ghana.

Participants Persons with HIV who were newly enrolled onto DTG.

Primary and secondary outcome measures Waist circumference, body mass index, blood pressure, fasting blood glucose and lipids were the primary outcomes measured at baseline, 3, 6, 12 and at 18 months follow-up to determine the incidence of MetS. MetS was defined using the Joint Consensus definition that combines the International Diabetes Federation and the National Cholesterol Education Programme Adult Treatment Panel III (ATP III) definitions. The Kaplan-Meier estimator was used to estimate the risk of developing MetS. The Cox proportional hazard model was used in estimating HRs.

Results Of 3664 PWH screened at baseline, 31.4% (1152/3664) had MetS. Of the remaining 2512 with no MetS at baseline, there were 960 incident cases of MetS over the 1.5 years follow-up. The estimated MetS incident rate is 384.2 (95% CI: 360.6 to 409.2) per 1000 person-years with a median time to development of MetS at 6 months (IQR; 3–12 months). Being female (adjsuted HR, aHR: 1.42, 95% CI: 1.19 to 1.70), age ≥50 years (aHR: 1.30, 95% CI: 1.12 to 1.51), having a comorbidity at baseline (aHR: 1.39, 95% CI: 1.12 to 1.51) and being overweight (aHR: 1.46, 95% CI: 1.25 to 1.71) and obese (aHR: 1.62, 95% CI: 1.36 to 1.93) were associated with higher risk of MetS development.

Conclusions The incidence of MetS was high among our patients, with elevated fasting blood sugar and elevated blood pressure being the most common developed MetS defining components. HIV programmes should institute targeted interventions at addressing central obesity to reduce the risk of MetS.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The lack of African population-specific cut-off values for waist circumference might have influenced the risk estimates observed.
⇒ Fasting blood sugar level was assessed using the same brand glucometers across all sites with capillary blood, which is not the gold standard, but a useful point of care test in the clinical setting.
⇒ Even though estimation of haemoglobin A1c levels is recommended to confirm the diagnosis of T2DM, this was not done in this study.
⇒ In our study, lifestyle factors and family history were not considered in determining incident metabolic syndrome (MetS) risk factors, which may have led to the overestimation of the incidence of MetS.
⇒ In spite of the limitations, the study was performed on a large representative population in Ghana, West Africa, adding to the diversity of knowledge on DTG and MetS within sub-Saharan Africa. The longitudinal nature and having established baseline components of MetS add to the robustness of the study findings.

INTRODUCTION/BACKGROUND

Persons living with HIV (PLHIV) have an increased risk of developing cardiovascular disease (CVD) partly attributable to the higher burden of metabolic syndrome (MetS). MetS refers to the clustering of cardiometabolic risk factors including arterial hypertension, abdominal obesity, defective glucose metabolism and dyslipidaemia.[1 2] There is an increase in the incidence of MetS among people living with HIV.[3–5] This is partly attributed to the antiretroviral (ARV) therapy (ART) induced longevity of PLHIV, exposing them to traditional risk factors for the condition.[6 7] Additionally, HIV has been shown to lead to a chronic inflammatory state that further exposes PLHIV to the development of MetS components.[8–10] This underscores

the need for specific policy interventions aimed at early detection, prevention and integrated care for HIV MetS and CVD. The use of antiretroviral therapy (ART) that includes protease inhibitors (PIs) and nucleoside-reverse-transcriptase-inhibitors (NRTIs) is also linked to the development of some MetS components, specifically glucose intolerance, weight gain and defective lipid metabolism including lipodystrophy.[11–13]

Globally, the prevalence of MetS among PLHIV has been estimated to range from 11% to 48%, with higher prevalence reported in sub-Saharan Africa (SSA).[14] In Ghana, two previous studies on MetS estimated prevalence between 23.6% and 57.3% among PLHIV.[15 16] Development of MetS among PLHIV increases the risk of type 2 diabetes mellitus, cancers, CVDs, non-alcoholic fatty liver disease and reduces their quality of life.[17–21] With these consequences, the high occurrence of MetS among PLHIV remains a threat to the gains made in HIV care over the years. To sustain the gains made and improve the quality of life for PLHIV's, findings from surveillance and monitoring of ART regimen and pharmacovigilance are continuously used to inform regimen changes.

The WHO recommended the use of dolutegravir (DTG)-based ARV regimen as the preferred treatment for all PLHIV in 2018 based on observed increased efficacy driven by high tolerability.[22–25] Despite the demonstrated efficacy and safety of DTG, there have also been reports of adverse effects including weight gain, dyslipidaemia, and increased risk of MetS components.[12 26–29] Ghana commenced the switch to DTG as a first-line regimen in September 2019 as per the WHO recommendations.[30] In light of the conflicting findings on the association between DTG and MetS,[28 31 32] it is important to explore this relationship as the DTG regimen is scaled up. In this study, we assessed the incidence of MetS in a Ghanaian cohort living with HIV and initiated on a DTG-based regimen as part of a larger national prospective cohort study.

METHODS

Study design and setting

We conducted a prospective cohort study from September 2020 to August 2022 among PLHIV. Patients were recruited from five high-burden ART facilities in Ghana representing teaching hospital, regional, district and faith-based settings. These were Korle Bu Teaching Hospital, St Martin's de Porres Hospital, Atua Government Hospital, Kumasi South Hospital and Kwesimintsim Hospital. These were purposively selected as they had high patient loads per the national data for each level of health service provision in Ghana.

Study population and eligibility

The study participants included PLHIV≥18 years (both ART naïve and ART experienced) initiated on a DTG-based regimen for the first time within the study period.

Exclusion criteria

PLHIV who were acutely ill; did not intend to engage with the clinic for at least 2 years; already on a DTG-based regimen from another ART site; or with pregnancy in the first trimester at baseline were excluded from the study.

Participant recruitment and follow-up

Patients included in the study were followed up for up to 72 weeks within which each person contributed person-time from DTG-based ART until the end of the study on 31 August 2022. Due to the observational nature of the study, patients identified with abnormal clinical outcomes (MetS or any components of MetS) were provided with the necessary appropriate interventions (lifestyle changes and medications) as deemed appropriate by their attending clinicians during clinic visits, and patients were expected to be adherent to the proposed interventions.

Data collection

At the point of enrolment (baseline), participant characteristics including sociodemographic (age, sex, level of education, ethnicity, marital status, religion and occupation), clinical (comorbidity, date of HIV diagnosis, HIV type, duration of ART, duration of current ART, previous ART combination, duration of previous ART, current DTG-based ART combination) were collected using a questionnaire (online supplemental table S1). These patient characteristics were identified from talking to patients, review of patients' records and measurements at the study sites. Clinical and laboratory tests included anthropometric (waist and hip circumference and blood pressure (BP)) and laboratory (fasting blood glucose (FBG) and serum lipid profiles). Any missing demographic data were confirmed from medical records review where necessary. These data were also collected at each follow-up period; 12, 24, 48 and 72 weeks, respectively.

Anthropometric and laboratory measurements

Height and weight were measured using a stadiometer (Seca 285 wireless stadiometer, SECA, Germany) and an electronic scale (PICOOC smart electronic scale, PICOOC, China), respectively, to the nearest 0.1 cm and 0.1 kg. Height was measured in metres (m) and weight was measured in kilograms (kg). Body mass index (BMI) was calculated using the weight and height data and was measured in kilogram per square metre (kg/m^2).

Waist circumference (WC) was measured to the nearest 0.1 cm. It was measured in the mid-axillary line at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest at the end of normal expiration using an inelastic tape measure. Normal WC was defined as <94 cm for males and <80 cm for females.

BP was measured using an electronic sphygmomanometer (Omron HEM 7124, OMRON, Vietnam). Patients sat in a straight back chair for 15 min before BP was measured on the left upper arm.[33] An average of two BP readings was taken 5 min apart and documented.[34 35] Normal BP was defined as <130/85 mm Hg). FBG was measured after

Table 1 Sociodemographic characteristics of the study participants

Participant characteristics	Frequency (n=2512)	Percentage (%)
Age: mean±SD	45.31±11.84	
<25	103	4.10
25–49	1559	62.06
50–59	556	22.13
>60	294	11.70
Sex		
Male	770	30.65
Female	1742	69.35
Ethnicity		
Akan	1075	42.79
Ga-Adangbe	791	31.49
Ewe	293	11.66
Northern tribes	319	12.70
Others	34	1.35
Marital status		
Single	530	21.10
Married	964	38.38
Divorced	324	12.90
Separated	120	4.78
Co-habitating	164	6.53
Widow/widower	410	16.32
Educational level		
No formal education	459	18.27
Primary	917	36.50
Secondary	949	37.78
Tertiary	187	7.44
Religion		
Christianity	2289	91.12
Islam	207	8.24
Traditionalists	10	0.40
Others	6	0.24
Occupational status		
Not employed	449	17.87
Employed	2013	80.14
Student	50	1.99
Any comorbid condition*		
No	2224	88.54
Yes	288	11.46

*Comorbidities were mainly hypertension, type 2 diabetes mellitus, asthma, gastro-oesophageal reflux disease and hepatitis.

a 12-hour overnight fast with a OneTouch Select Simple glucometer using capillary blood.[36 37] Normal FBG was defined as <5.6 mmol/L (100 mg/dL).

For blood lipid measurements, about 4 mL of blood was taken from participants' antecubital fossa after a 12-hour overnight fast for analysis.[38] The lipids assessed included total serum cholesterol, high-density lipoprotein (HDL) and triglycerides. Normal total serum cholesterol was defined as ≤5.2 mmol/L (200 mg/dL) for both males and females. Normal HDL-cholesterol was defined as ≥1.29 for females and ≥1.03 mmol/L (40 mg/dL) for males. Normal triglycerides were defined as <3.88 mmol/L (150 mg/dL) for both males and females.

The main study outcome of MetS was defined using the Joint consensus definition that combines the International Diabetes Federation (IDF) and the National Cholesterol Education Programme Adult Treatment Panel III (NCEP/ATP III) definitions as having any three of the following[33]; abnormal WC of >80 cm in women and >94 cm in men (adjusted for the African population), triglycerides 150 mg/dL (3.88 mmol/L) or greater or on treatment for dyslipidaemia, HDL-cholesterol <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women or on treatment for dyslipidaemia, BP 130/85 mm Hg or greater or on treatment for hypertension, FBG of 100 mg/dL (5.6 mmol/L) or greater or on treatment for diabetes. Once a patient is identified to have MetS, follow-up ends for that patient or the data for the patient is censored for the study; however, the patient continues to receive clinical care by their physicians.

Quality assurance

Data collectors were trained on the use of the electronic instruments and on the study procedures. The documentation, storage and transport of blood samples were done by trained personnel. All blood sample analyses were conducted in an ISO-accredited laboratory (ISO 15189:2012). All study instruments were calibrated by the Korle Bu Hospital Biomedical Engineering department.

Data management and analysis

Data collected were downloaded in Microsoft Excel format from Kobo Collect, cleaned and imported to STATA V.17 for statistical analysis. BMI was calculated using the standard formula of weight (kg)/height (m) squared and categorised as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–30 kg/m^2) and obese (>30 kg/m^2). Frequencies and percentages were used to present summary statistics for categorical variables. For continuous variables, the mean and SD were reported for normally distributed data, whereas the median and IQRs were reported for skewed data.

Prevalence of MetS at baseline was calculated as the number of participants with three or more MetS components at baseline divided by the total number of participants screened. The incidence rate of MetS was estimated by dividing the total number of new MetS cases among MetS-free individuals followed up by the total number of person-years at risk. Missing data related to any number of MetS defining components occurring at any time during

Table 2 Clinical characteristics of study participants

Participant characteristics	Frequency (n=2885)	Percentage (%)
BMI (kg/m^2)		
Mean±SD	24.41±5.35	
Underweight (<18.5)	236	9.39
Normal (18.5–24.9)	1310	52.15
Overweight (25–30)	583	23.21
Obesity (>30)	383	15.25
Type of HIV		
HIV-1	2435	96.93
HIV-2	15	0.60
HIV1/HIV2	62	2.47
ART status		
ART naive	260	10.35
On ART	2252	89.65
Period of HIV infection		
Median (LQ–UQ)	4.77 (2.30–5.40)	
<5 years	1158	46.67
5–10 years	717	28.90
>10 years	606	24.43
Duration on ART		
Median (LQ–UQ)	4.35 (2.70–5.00)	
<5 years	988	45.93
5–10 years	706	32.82
>10 years	457	21.25
NRTI regimen		
Tenofovir based	2489	99.08
Abacavir based	6	0.24
Zidovudine based	17	0.68
Blood pressure		
Normal	1689	67.24
Abnormal	823	32.76
Individual MetS components	Median (LQ–UQ)	
Waist circumference (cm)	77.00 (62.00, 87.00)	
Fasting blood sugar level (mmol/l)	5.70 (5.20, 6.30)	
HDL cholesterol (mg/dL)	1.50 (1.20, 1.80)	
Triglycerides (mg/dL)	0.87 (0.66, 1.18)	
Systolic blood pressure mm Hg	118.00 (107.00, 132.00)	
Diastolic blood pressure mm Hg	76.00 (69.00, 85.00)	

ART, antiretroviral therapy; BMI, body mass index; HDL, high-density lipoprotein; LQ, lower quartile; MetS, metabolic syndrome; NRTI, nucleoside-reverse-transcriptase-inhibitor; UQ, upper quartile.

the period of participation in the study was presumed to indicate no MetS.

The survival function of developing MetS was calculated using the Kaplan-Meier estimator. The Nelson-Aalen cumulative hazard function was provided for each specific study time point. The log-rank test was used to assess the differences in the survival function related to the development of MetS among various background characteristics. Association between time to development of MetS was measured using the Cox proportional hazard model with robust SEs. Due to the small number of people who developed elevated triglycerides during follow-up, the continuous form of this variable was used in the final model. The HR with its 95% CI was reported. 62 out of 961 events in the 2512 observations had interval censoring. Four additional models were fitted in addition to the standard Cox proportional hazard model with robust SE ignoring the interval censoring. Poisson model with robust SE 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 SE, Poisson model with robust SE and exposure time using midpoint time of interval-censored data. Parametric models for interval-censored survival-time data with exponential distribution link and robust SE were all similar to results from the standard Cox proportional hazard model with robust SE ignoring the interval censoring. The level of significance for all statistical tests was 5%.

Patient and public involvement

There was engagement with the National HIV/AIDS Control Programme (NACP) of the Ghana Health Service (GHS) and the staff and management of the facilities involved in the study. The NACP was involved in the design, conduct and reporting of the study. Patients were not involved in the design, or conduct, or reporting of the study. However, they had the study findings disseminated to them at the outpatient departments at study sites. Dissemination was also done to the NACP-GHS and to the staff and management of the study sites.

RESULTS

Sociodemographic characteristics of the study participants

Of the 3664 participants screened at baseline, 31.4% (1152/3,664) had MetS and were excluded from the study. Out of the remaining 2512 with no MetS, the average age was 45.3±11.8 years, with the majority of them (62.1%, 1559/2512) being within 25–49 years and 69.4% (1742/2512) were females. About 81.3% (2053/2512) of the patients had at least primary-level education and 38.4% (964/2512) were married (table 1).

Table 3 Incidence of metabolic syndrome (MetS) and MetS components developed among the study participants

Individual MetS components	Baseline n (%)	3 months n (%)	6 months n (%)	12 months n (%)	18 months n (%)
Elevated fasting blood glucose	1409/2509 (56.16)	1225/2072 (59.12)	923/1661 (55.57)	975/1376 (70.86)	597/1055 (56.56)
High blood pressure	845/2512 (33.64)	1051/2270 (46.30)	761/1776 (42.85)	628/1464 (42.90)	622/1259 (49.40)
Abnormal waist circumference	764/2495 (30.62)	716/2055 (38.83)	487/1663 (29.28)	403/1378 (29.25)	300/1082 (27.73)
Low HDL	606/2511 (24.13)	798/2055 (38.83)	515/1654 (31.14)	411/1367 (30.07)	297/1000 (29.70)
High triglyceride	4/2338(0.17)	3/2055 (0.15)	12/1654 (0.73)	2/1367 (0.15)	1/1000 (0.1)

HDL, high-density lipoprotein; MetS, metabolic syndrome.

Clinical characteristics of the study participants

The majority of study participants had normal BMI at baseline 52.2% (1310/2512) with overall mean BMI (±SD) of 24.4 (±5.35) kg/m^2. Almost all (96.9%, 2435/2512) of the participants had HIV-1 and the majority (89.7%, 2252/2512) were ART exposed at baseline. Among the ART exposed, close to half (46.0%, 988/2151) had been on the regimen for less than 5 years (table 2).

Incidence of MetS among study participants

The total number of person years contributed by the 2512 participants was 2497.8 over the one and a half year period. The cumulative incidence of MetS was 38.2% (95% CI: 36.3% to 40.1%) and the incidence rate was 384.2 (95% CI: 360.6 to 409.2) per 1000 person-years. The median time to the development of MetS was 6 months (IQR 3–12 months). The number of MetS components among participants at baseline was 4142 with high BP as the most common MetS component at 37.0% (1532/4142). At baseline, 49% (1407/2885) of participants had two components of MetS; 40% (1143/2885) had one component and 11% (335/2885) had no MetS components. Incident MetS components developed after follow-up were 10 637 with high fasting blood sugar (FBS) and high BP being the most developed incident MetS components after follow-up at 38.9% (4139/10 637) and 30.2% (3216/10 637). respectively. Across the MetS components, the majority of incident cases were developed in the third and sixth months of follow-up, with a decreasing trend in the incident cases as follow-up time increased (table 3).

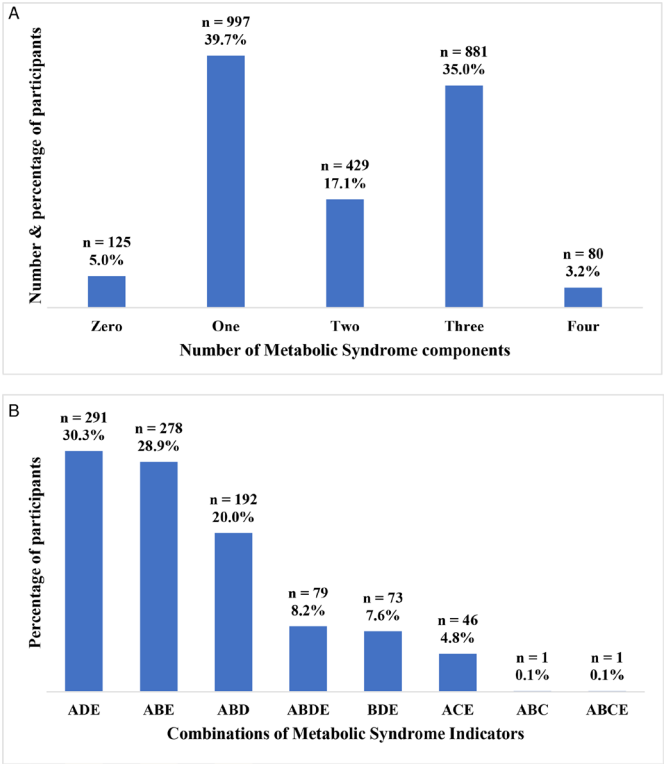

Figure 1 (A) Distribution of number of MetS components among PLHIV by month 18 postinitiation on DTG-based treatment, 2020–2022. (B) Distribution of combinations of MetS components among PLHIV initiated on DTG-based treatment, 2020. A: Fasting Blood Sugar, B: High Density Lipoprotein, C: Triglyceride, D: waist circumference, E: Blood Pressure. DTG, dolutegravir; MetS, metabolic syndrome; PLHIV, persons living with HIV.

Figure 1A shows the distribution of number of abnormal MetS Components identified at the end of the study. Five per cent (125/2512) of the participants had no abnormal MetS component, while about four in every ten (39.7%, 997/2512) participants had only one abnormal MetS component. Close to one-third of the participants had three abnormal MetS components. Of the 961 people who developed MetS (those with ≥3 abnormal MetS components), the most common combination used to diagnose MetS was elevated FBS, above normal WC and elevated BP (30.3%, 291/961), followed by elevated FBS, low and elevated (28.9%, 278/961). About 8.3% (80/961) had four of the metabolic abnormalities and no one had all five abnormalities (figure 1B).

Females had comparatively higher risk of developing MetS compared with males. The risk of developing MetS was higher among those aged 50 years or more compared with those 18–49 years. Also, participants with underlying diseases had a higher chance of developing MetS early in the follow-up period compared with those without underlying conditions (figure 2).

Factors associated with incident MetS among PLHIV on DTG-Based regimen, Ghana, 2022

After adjusting for ethnicity, marital status, educational status, occupation and duration of HIV diagnosis, the

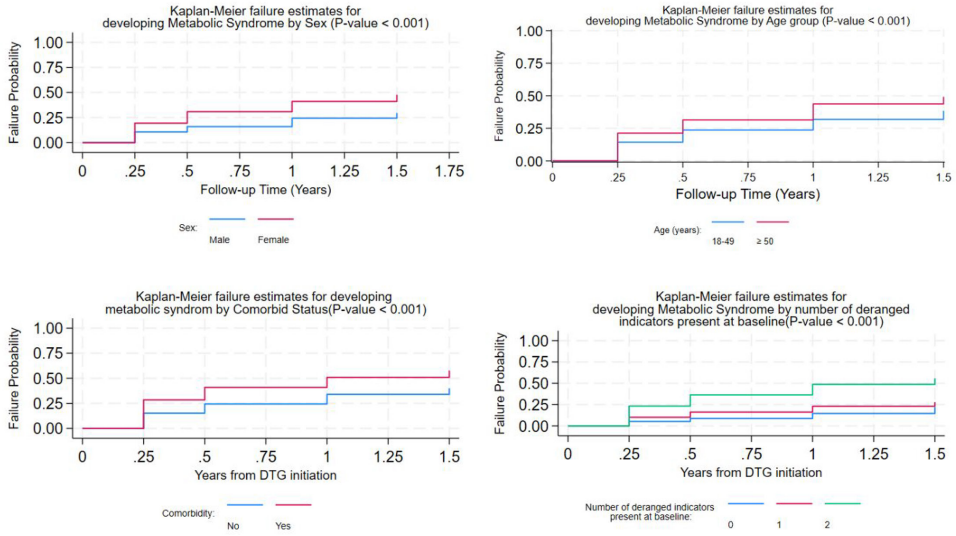

Figure 2 Kaplan-Meier failure estimates for developing metabolic syndrome among PLHIV enrolled on DTG. DTG, dolutegravir; PLHIV, persons living with HIV.

hazard of MetS was 30% higher for those aged 50 years and above compared with those aged 18–49 years (adjusted HR, aHR: 1.30, 95% CI: 1.12 to 1.51). Females had a 42% higher hazard of developing MetS compared with males (aHR: 1.42, 95% CI: 1.18 to 1.70). Additionally, the adjusted model showed a significant association between incident MetS and presence of comorbidity (aHR: 1.39, 95% CI: 1.15 to 1.68), being overweight (aHR: 1.46, 95% CI: 1.25 to 1.71), obese (aHR: 1.62, 95% CI: 1.36 to 1.93) and having abnormal WC (aHR: 3.02, 95% CI: 2.54 to 3.60). Compared with those with normal BMI, abnormal BP level (aHR: 1.93, 95% CI: 1.63 to 2.30), abnormal FBS (aHR: 1.32, 95% CI: 1.13 to 1.55), abnormal HDL cholesterol level (aHR: 1.79, 95% CI: 1.47 to 2.18) and a unit increase in triglyceride level was associated with a 24% increase in the hazard of having MetS (aHR: 1.24, 95% CI: 1.10 to 1.40) (table 4).

DISCUSSION

We sought to determine the incidence of MetS in a cohort of HIV positive adults initiated on DTG-based ART regimen in Ghana. After 18 months follow-up, we recorded overall MetS incidence of 384.2 per 1000 person-years. Of the five MetS defining components, close to 40% developed incident FBS derangement, almost a third developed high BP at the end of follow-up and more than half of those who had MetS had a combination of high BP, abnormal WC and elevated FBS. Older age, female sex, being overweight or obese and having a comorbidity were significant risk factors for incident MetS.

After initiation onto the DTG-based regimen, 961 MetS-free individuals developed MetS, giving a cumulative hazard of over 38%. The overall incidence rate of 384.2 per 1000 person-years estimated in our study was much higher than the incidence of 85 per 1000 person-years and 11.8 per 1000 person-years that were recorded in other incident cohorts conducted in the USA and Asia.[39 40] The cumulative hazard of 38% was also higher than the pooled prevalence of MetS among PLHIV in SSA of 21%–23.42% from a systematic review of 25 studies.[41] The differences may be due to a number of factors. In the US cohort study that was conducted in 2012, the same Joint definition used in our study was applied. However, increasing life expectancy of PLHIV's, prolonged duration on ART and increasing incidence of NCDs among the general population and PLHIV's may be the reasons for the differences in reported incidence.[42–47] In the systematic review from SSA, the definitions used for MetS were that of the NCEP/ATP III criteria and the IDF criteria which were different from our Joint definition and therefore could also contribute to the differences in MetS burden being reported.[41]

In the Asian study conducted in 2022, they defined MetS using the IDF criteria that holds above normal WC as a requirement for MetS diagnosis compared with the more sensitive joint criteria used in our study.[1 48] Additionally, the Asian study included PLHIV from the IeDEA observational cohort study where routine facility data collated over years was analysed longitudinally, which authors indicated may have led to missing some MetS cases, while our study was a planned prospective study.[40] The recorded high incidence of MetS in our study population is of concern due to the established consequences of MetS, which include excess morbidity and mortality due to CVDs, cancers, non-alcoholic fatty liver disease and reduced quality of life among PLHIVs.[17–21]

Patients 50 years and above had a higher risk of developing MetS compared with those between 18 and 49 years. This finding is consistent with the results of studies conducted in Southern Ethiopia, South Africa and Kenya where increasing age increased the risk of MetS.[18 49–53] This finding is generally not surprising as it aligns with the consequences of ART-induced longevity among PLHIV's that increases their risk for chronic diseases.[54]

Table 4 Baseline factors associated with incident MeTS among PLHIV on DTG, Accra, 2022

	Person-years	No of persons with MetS	Incidence rate (per 1000 PY), (95% CI)	aHR (95% CI)	P value
Overall	**2501.50**	**961**	**384.2 (360.6 to 409.2)**	_	_
Age (in years)					
18–49	1675.75	569	339.55 (312.77 to 368.63)	1	
≥50	825.75	392	474.72 (429.98 to 524.12)	1.30 (1.12 to 1.51)	0.001
Sex					
Male	845.50	204	241.28 (210.34 to 276.77)	1	
Female	1656.00	757	457.13 (425.69 to 490.88)	1.42 (1.18 to 1.70)	<0.001
HIV type					
HIV-1	2416.25	926	383.24 (359.33 to 408.73)	1	
HIV-2	16.25	7	430.77 (205.36 to 903.58)	1.05 (0.53 to 2.08)	0.884
HIV1/HIV2	69.00	28	405.80 (280.19 to 587.72)	1.00 (0.68 to 1.47)	0.998
NRTI regimen					
Tenofovir	2476.25	954	385.26 (361.57 to 410.50)	1	
Abacavir	7.25	2	275.86 (68.99 to 1103.02)	1.32 (0.68 to 2.56)	0.412
Zidovudine	18.00	5	277.78 (115.62 to 667.37)	0.60 (0.26 to 1.40)	0.236
Comorbidity*					
No	2245.75	803	357.56 (333.67 to 383.17)	1	
Yes	255.75	158	617.79 (528.60 to 722.04)	1.39 (1.15 to 1.68)	0.001
BMI					
Underweight	237.00	50	210.97 (159.90 to 278.36)	0.78 (0.56 to 1.07)	0.125
Normal	1403.50	399	284.29 (257.72 to 313.60)	1	
Overweight	548.75	282	513.90 (457.28 to 577.51)	1.46 (1.25 to 1.71)	<0.001
Obesity	312.25	230	736.59 (647.29 to 838.21)	1.62 (1.36 to 1.93)	<0.001
Blood pressure					
Normal	1707.75	575	336.70 (310.27 to 365.38)	1	
Abnormal (high)	793.75	386	486.30 (440.13 to 537.31)	1.93 (1.63 to 2.30)	<0.001
FBS					
Normal	1030.00	444	431.07 (392.78 to 473.09)	1	
Abnormal (elevated)	1470.75	516	350.84 (321.84 to 382.46)	1.32 (1.13 to 1.55)	<0.001
Waist circumference					
Normal	1879.75	487	259.08 (237.06 to 283.14)	1	
Abnormal	607.75	466	766.76 (700.21 to 839.64)	3.02 (2.54 to 3.60)	<0.001
HDL cholesterol					
Normal	1973.00	745	377.60 (351.43 to 405.71)	1	
Abnormal	528.25	215	407.00 (356.08 to 465.21)	1.79 (1.47 to 2.18)	<0.001
Cholesterol					
Normal	1664.75	608	365.22 (337.31 to 395.44)	1	
Abnormal	836.50	352	420.80 (379.06 to 467.14)	0.82 (0.71 to 0.95)	0.007
Triglycerides†	na	na	na	1.24 (1.10 to 1.40)	0.001

*Comorbidities were mainly hypertension, type 2 diabetes mellitus, asthma, gastro-oesophageal reflux disease.
†The continuous form the variable was used in the analysis as over 99.8% of the participants were classified to have normal values.
ART, antiretroviral therapy; BMI, body mass index; DTG, dolutegravir; FBS, fasting blood sugar; HDL, high-density lipoprotein; MetS, metabolic syndrome; na, not available; NRTI, nucleoside-reverse-transcriptase-inhibitor; PLHIV, persons living with HIV.

Females had an increased risk of developing MetS compared with males. Our findings were consistent with the findings of other studies conducted in Kenya and the USA where females had an increased risk of developing MetS compared with males.[50 55 56] This was, however, inconsistent with findings from a study in Poland where males were reported to have a higher risk of developing MetS.[57] The disparity in findings could be due to differences in the study designs which were cross-sectional compared with our longitudinal design and also differences in health-seeking behaviour among men and women across various contexts.[58–60]

Consistent with the literature, each component used to define MetS in this cohort increased the incidence risks individually. Their level of influence, however, differed. While an abnormal WC increased MetS risk by almost three times, the risks doubled for abnormalities in BP, increased by one and a half for abnormalities in FBG and HDL cholesterol, and slightly more than one for triglycerides. The almost three times risk increase of MetS from above normal WC supports the consideration of this component as a core manifestation of MetS. Other studies from South-West Nigeria and China found WC was a higher predictor of MetS compared with the other components.[61–63] It is also in line with the call by the American College of Cardiology[64] and the International Chair on Cardiometabolic Risk working group on visceral obesity[65] for WC to be seen as a routine vital sign in clinical practice.

Following exposure to DTG, the BMI of participants showed an increased MetS risk gradient. Compared with those who were underweight, incident MetS risk increased for normal, overweight and obese by 1.6 times, 2.4 times and 2.6 times, respectively. This is consistent with the finding that increased WC is associated with increased BMI and MetS risk.[66]

Despite conflicting reports on the effect of abacavir on the development of MetS, our findings showed a 32% increased risk of developing the condition among the study participants on abacavir compared with those on other NRTIs, though this was not statistically significant.[67] Abacavir-containing regimens are noted to contribute to dyslipidaemia.[68] It is worthy to mention that the majority of patients on Abacavir in our study had eGFR of less than 60 mls per minute. It is not clear how this and the small number of participants on abacavir-containing regimens influenced this finding. Therefore, this result should be interpreted with caution and further explored in studies with larger sample size.

Having type 2 HIV increased the hazard of developing MetS by 5% among the study participants. The numbers of patients with type 2 HIV were few. More significant is the fact that they had been on PIs. Their prior exposure to PIs, known to increase the risk of MetS through lipodystrophy, dyslipidaemia and insulin resistance, might have accounted for this finding.[13] DTG has been reported to increase the risk of high BP,[69] increase fasting glucose levels[70] and decrease HDL levels, which are all likely to increase the risk of MetS in PLHIV.

Limitations of the study

Data on other known risk determinants for MetS, such as lifestyle factors, were not considered in determining incident MetS risk factors. The lack of population-specific cut-off values for WC might also have influenced the risk estimates observed as the European thresholds adjusted for the African population were used. In our study, most of the participants had two of the MetS components at baseline. This may have led to overestimation of the incidence of MetS in our study. In addition, high glucose levels were identified in this study. The study determined FBS 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. Haemoglobin A1c levels were not conducted as part of high glucose levels confirmation, as this is not done in our general population for diagnosis of T2DM. Despite these limitations, the study was performed on a large representative population in Ghana, West Africa, adding to the diversity of knowledge on DTG and MetS within SSA. The longitudinal nature and having established baseline components of MetS add to the robustness of the study findings.

CONCLUSIONS

In our cohort of PLHIV initiated on DTG, we recorded a high incidence of MetS with elevated FBS and elevated BP as the most common MetS defining component developed during follow-up. Older age, being male, all BMI classifications above normal WC, elevated BP, elevated FBS and increased triglycerides were identified risk factors for incident MetS in this Ghanaian population.

RECOMMENDATIONS

We recommend routine clinical monitoring and interpretation of all MetS components among PLHIV's by HIV service providers, with priority given to measurement of WC and BP. This is necessary for the prevention of MetS and reduction of CVD through the implementation of targeted risk reduction interventions, with the early identification and appropriate management. Studies to determine African specific cut-off points for WC are recommended to aid in the standardisation of MetS diagnosis.

Author affiliations
[1]Department of Population, Family, Reproductive Health, School of Public health, University of Ghana, Accra, Ghana
[2]Department of Medicine, Korle Bu Teaching Hospital, Accra, Ghana
[3]Ghana Field Epidemiology and Laboratory Training Programme, Department of Epidemiology and Disease Control, School of Public Health, University of Ghana, Accra, Ghana
[4]National AIDS &STI Control Programme, Ghana Health Service, Accra, Ghana
[5]Department of Biostatistics, School of Public Health, University of Ghana, Accra, Ghana

[6]National Malaria Elimination Program, Ghana Health Service, Accra, Ghana
[7]Department of Medicine & Therapeutics, University of Ghana Medical School, Accra, Ghana

Correction notice This article has been corrected since it was first published. Figure 1 caption has been updated.

X Ernest Kenu @ErnestKenu

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ORCID iD
Vincent Ganu http://orcid.org/0000-0001-8649-4344

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