Original Article

Prevalence and Determinants of Metabolic Syndrome Among People with HIV Using Antiretroviral Medications in a Referral Hospital in Southern Nigeria

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ABSTRACT

HIV infection and its treatment, in addition to a longer lifespan, may raise the risk of metabolic syndrome (MetS) among people living with HIV (PLWH). MetS is a cluster of interrelated cardio-metabolic abnormalities linked to an elevated risk of cardiovascular events and mortality. This study aimed to assess the prevalence and risk factors of MetS in PLWH receiving antiretroviral therapy at a referral hospital. This cross-sectional study was conducted among 354 PLWH in the HIV clinic at the University of Uyo Teaching Hospital, Nigeria, from April to June 2024. Participants' blood pressure and anthropometric measurements were obtained following standard procedures. Fasting plasma glucose, serum concentrations of total cholesterol, high-density lipoprotein cholesterol, and triglycerides were also measured. Data were analysed using SPSS version 25.0, with $p < 0.05$ indicating statistical significance. Participants were mostly female (66.7%), with a mean age of 48.5±9.8 years. The majority (66.1%) of the participants were using tenofovir-lamivudine-dolutegravir antiretroviral regimen. The prevalence of MetS was 18.1% and 24.0% based on the revised National Cholesterol Education Programme-Adult Treatment Panel III (NCEP-ATP III) and Joint Interim Statement (JIS) criteria, respectively. Body mass index ($p < 0.001$) and antiretroviral therapy ($p < 0.05$) were significant predictors of MetS, as defined by both criteria. MetS appears to be common among the participants. Regular screening for MetS, education on healthy lifestyles, and careful selection of antiretroviral therapy are crucial for PLWH in order to reduce the incidence of MetS and their risk of cardiovascular events and mortality.

Keywords: Antiretroviral therapy, Metabolic syndrome, People living with HIV, Prevalence, Nigeria.

INTRODUCTION

Life expectancy of people living with HIV (PLWH) has significantly increased since the introduction of combination antiretroviral therapy. This has resulted in an increase in the incidence and prevalence of cardio-metabolic disorders and other non-communicable diseases linked to aging and the impact of HIV and its treatment.[1,2] Metabolic syndrome represents a clustering of interrelated risk factors for cardiovascular disease, type 2 diabetes, nonalcoholic fatty liver disease, infertility, several cancers, dementia and other diseases.[3-5] People with the metabolic syndrome are twice as likely to die from and three times as likely to have a heart attack or stroke compared to those without the syndrome.[6]

Components of the metabolic syndrome include high blood pressure, insulin resistance with or without glucose intolerance/hyperglycaemia, hypertriglyceridaemia, reduced high-density lipoprotein cholesterol (HDL-C), and abdominal obesity. There are no well-accepted criteria for the diagnosis of the metabolic syndrome.[3] Various groups have proposed different clinical criteria for diagnosing the syndrome, including the World Health Organisation (WHO),[7] the European Group for the Study of Insulin Resistance (EGIR),[8] National Cholesterol Education Programme (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III),[3] and the International Diabetes Federation.[6] Although all groups agreed on the core components of the metabolic syndrome—obesity, insulin resistance, dyslipidaemia and hypertension, there are minor discrepancies mostly with respect to measure for central obesity.[5,6] In 2009, a meeting among major groups aimed to harmonise criteria for identifying patients with the syndrome, leading to the proposal of common criteria: the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity (JIS). The JIS acknowledges that the risk associated with a particular waist measurement will vary in different populations and establishes the diagnosis of the syndrome if three of the following five criteria are present: abdominal obesity (as determined by population- and country-specific waist circumference cut points); elevated triglycerides, or drug treatment for elevated triglycerides; reduced HDL-C, or drug treatment for reduced HDL-C; elevated blood pressure, or antihypertensive drug treatment in an

individual with a history of hypertension; and impaired fasting glucose, or drug treatment of elevated glucose or diabetes.[5]

The third Report of the NCEP-ATP (NCEP-ATP III)[3] is one of the most widely used criteria for identifying an individual with metabolic syndrome.[9] It requires the presence of at least three of the following five criteria to establish the diagnosis of the syndrome: abdominal obesity, elevated triglycerides, reduced HDL-C, elevated blood pressure, and impaired fasting glucose.[3,10] Other components of the metabolic syndrome—insulin resistance, a pro-inflammatory state, and a prothrombotic state—cannot be identified by routine clinical evaluation. However, in the presence of abdominal obesity, they are often present.[3]

Although the underlying causes of the metabolic syndrome are (central) obesity/overweight, insulin resistance, physical inactivity, and genetic factors,[3,6] both traditional and HIV-related factors, such as antiretroviral drugs and HIV infection itself, have been shown to contribute to the prevalence of components of the syndrome among PLWH.[11] A higher prevalence of metabolic syndrome or some of its components (hypertension, hyperglycaemia/ diabetes, dyslipidaemia) has been reported among PLWH on antiretroviral therapy compared with treatment-naïve PLWH and the general population.[12-15] PLWH, particularly those are more likely to develop features of the metabolic syndrome when exposed to antiretroviral therapies such as protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs).[16-18] The NRTIs affect fat distribution (both lipohypertrophy and lipoatrophy), which is associated with insulin resistance.[16,18] The insulin resistance accompanying the metabolic syndrome is one of the causes of type 2 diabetes.[16] As a result, regular screening for diabetes/pre-diabetes, monitoring and management of lipids and other cardiovascular risk factors among PLWH are recommended.[11,16] Studies that assess the prevalence of metabolic syndrome among PLWH are sparse in southern Nigeria, particularly since the introduction of dolutegravir-based first-line antiretroviral therapy. Therefore, this study aimed to determine the prevalence and risk factors of the metabolic syndrome among PLWH using antiretroviral medications at a major referral hospital in Akwa Ibom State, Nigeria.

MATERIALS AND METHODS

Study design, setting and participants

This was a cross-sectional study conducted at the HIV clinic of the University of Uyo Teaching Hospital, Uyo, Akwa Ibom State, Nigeria. Akwa Ibom State is one of the three states with the highest prevalence of HIV infection in the country.[19,20] The University of Uyo Teaching Hospital is a 500-bed capacity hospital located in Uyo, the state's capital, and is the major referral hospital in the state. At the time of data collection, there were approximately 3800 registered treatment-experienced PLWH at the hospital, many of whom had had their treatments devolved to other centres. Assuming a 95% confidence level, a 5% margin of error, and a 32% prevalence of metabolic syndrome in PLWH from a previous study,[14] the minimum sample size was calculated to be 334 using the formula: $n = Z^2(P)(1-P)/E^2$. However, to account for a possible 10% non-response and boost the statistical power of the analysis, 367 participants were targeted for the study. Ambulatory adult patients aged 30 years or older with a physician-documented HIV diagnosis who had been using antiretroviral drugs for at least six months, who had had an overnight fast of about 12 hours and provided written informed consent to participate in the study were eligible. Purposive sampling method based on these inclusion criteria was adopted in recruiting the participants.

Data collection

After the daily health talk delivered at the HIV clinic, the principal investigator explained the study's objectives to potential participants and invited them to participate in the study. Two research assistants extracted information, including age, medical history, antiretroviral regimen being used, and length of time they had been on antiretroviral therapy, from their case notes and documented it in a form designed specifically for the study. An automatic upper arm blood pressure monitor (Omron Healthcare Co., Ltd.) was used to measure participants' blood pressure in a sitting position. Before taking the first measurement, each participant was allowed to sit quietly for at least 5 minutes. The blood pressure was determined by averaging two measurements taken approximately one minute apart. The participants' weight and height were measured in an upright position, without shoes, using a calibrated digital weighing scale and stadiometer (Seca gmbh & co. kg, Hamburg, Germany). The body mass index (BMI) was determined as the ratio of weight (in kilograms [kg]) to the square of height (in meters squared [m^2]). The waist circumference was measured horizontally at the narrowest point between the lower end of the rib cage and the iliac crest, using a flexible inelastic tape measure. The participants were then taken to the hospital's HIV and Testing Services laboratory, where 2 ml of venous blood was aseptically collected into fluoride oxalate vacutainer tubes and 4 ml of venous blood into plain vacutainer tubes for the determination of fasting plasma glucose and lipid profile, respectively. Fasting plasma glucose was determined by the glucose oxidase method. Serum concentrations of total cholesterol, high density lipoprotein (HDL)-cholesterol, and triglycerides were determined by an enzymatic colorimetric method using commercially available reagents from Spectrum Diagnostics, Ismailia, Egypt. These assays were performed using an ultraviolet spectrophotometer (Bauer, Germany) in the chemical pathology laboratory at the University of Uyo Teaching Hospital.

Criteria for identifying metabolic syndrome

In the present study, we identified participants with metabolic syndrome based on the revised NCEP-ATP III definition,[3,10] and that of the JIS,[5,10] Based on the NCEP-ATP III definition, we identified individuals with metabolic

syndrome if any three of the following five criteria were present: abdominal obesity, defined as a waist circumference >102 cm (for men) or >88 cm (for women); triglycerides ≥ 150 mg/dL; HDL-C <40 mg/dL (in males) or < 50 mg/dL (in females); blood pressure ≥ 130/85 mmHg; and fasting glucose ≥100 mg/dL.[3,10] For the JIS definition, the presence of any three of the following criteria qualified an individual for metabolic syndrome: abdominal obesity, using the IDF cut points for sub-Saharan Africa, which are ≥94 cm for men and ≥80 cm for women; triglycerides ≥ 150 mg/dL, or drug treatment for elevated triglycerides; HDL-C <40 mg/dL (in males) or < 50 mg/dL (in females) or drug treatment for reduced HDL-C; blood pressure ≥130/85 mmHg, or antihypertensive drug treatment in an individual with a history of hypertension; and fasting glucose ≥100 mg/dL, or drug treatment of elevated glucose/diabetes.[5,10]

Data analysis

The data were analysed using SPSS version 25.0 (IBM Corp., Amonk, NY). Descriptive statistics (mean with standard deviation, frequency with percentage) were used to summarise patients' demographic and clinical data. Binary logistic regression analysis was performed to identify the predictors of metabolic syndrome (the outcome variable) with sex, age, BMI, type of antiretroviral therapy, and duration on antiretroviral therapy serving as independent variables. The significance level for all analyses was set at $p < 0.05$.

Ethical considerations

This study was performed in compliance with the principles of the Declaration of Helsinki. Approval to conduct the study was obtained from the Health Research Ethics Committee of University of Uyo Teaching Hospital (UUTH/AD/S/96/VOL.XXI/852, dated March 8, 2024).

Written informed consent was obtained from all the participants and/or their legal representatives after assuring them of confidentiality.

RESULTS

A total of 367 PLWH were invited to participate in the study; however, 358 agreed to participate and were recruited, giving a response rate of 97.5%. Those that declined gave reasons such as not being interested or being in a hurry. Four of the 358 participants had missing or incomplete laboratory results; thus, 354 participants were included in the final analysis. The participants were predominantly female (66.7%) and had a mean age of 48.5±9.8 years. The majority (66.1%) were on the first-line regimen: tenofovir-lamivudine-dolutegravir. (Table 1)

Table 1 Demographic and Clinical characteristics of Participants

Variable	Mean	Standard deviation
Age (years)	48.5	9.8
BMI (kg/m^2)	24.9	5.4
Waist circumference (cm)	80.6	12.5
Systolic BP (mmHg)	130.1	20.9
Diastolic BP (mmHg)	80.7	12.2
Duration on ART (months)	139.2	71.0
	Frequency	**Percent**
Sex		
Male	118	33.3
Female	236	66.7
Antiretroviral therapy		
Tenofovir* + lamivudine + dolutegravir	234	66.1
Abacavir + lamivudine + dolutegravir	104	29.4
Tenofovir* + lamivudine + Atazanavir/ritonavir	8	2.3
Abacavir + lamivudine + Atazanavir/ritonavir	8	2.3
Regimen line		
First line	338	95.5
Second line	16	4.5

*Tenofovir disoproxil fumarate

Prevalence of metabolic syndrome and component disorders among participants

The prevalence of metabolic syndrome among the participants was 18.1% and 24.0% based on the revised NCEP-ATP III and JIS criteria, respectively. About half (52.3%) of the participants had elevated blood pressure; only 5 (1.4) had been previously diagnosed with diabetes. According to the revised NCEP-ATP III and JIS criteria, 285 (80.5%) and 297 (83.9%) of the participants, respectively, had at least one component of metabolic syndrome. (Table 2)

Table 2 Prevalence of metabolic syndrome and component disorders among participants (N = 354)

Variable	Frequency	Percent
Prevalence of the MetS (NCEP-ATP III)	64	18.1
Prevalence of the MetS (JIS)	85	24.0
Abdominal obesity (NCEP-ATP III)		
Men (waist circumference > 102 cm) *(n = 118)*	4	3.4
Women (waist circumference > 88 cm) *(n = 236)*	65	27.5
Abdominal obesity (JIS)		
Men (waist circumference ≥94 cm) *(n = 118)*	15	12.7
Women (waist circumference ≥ 80 cm) *(n = 236)*	122	51.7
Triglycerides (≥ 150 mg/dL)	69	19.5
HDL-cholesterol		
Men (< 40 mg/dL) *(n = 118)*	23	19.5
Women (< 50 mg/dL) *(n = 236)*	82	34.7
Fasting blood glucose (≥ 100 mg/dL)	97	27.4
Blood pressure (≥ 130/85 mmHg)	185	52.3
Previously diagnosed with diabetes mellitus	5	1.4
Previously diagnosed with hypertension	52	14.7
No. of components of MetS present (NCEP-ATP III)		
None	69	19.5
One	125	35.3
Two	96	27.1
Three	45	12.7
Four	18	5.1
Five	1	0.3
No. of components of MetS present (JIS)		
None	57	16.1
One	109	30.8
Two	103	29.1
Three	61	17.2
Four	21	5.9
Five	3	0.8

HDL high density lipoprotein; *JIS* Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity; *MetS* metabolic syndrome; *NCEP-ATP III* Third Report of the National Cholesterol Education Programme Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.

Table 3: Binary logistic regression to determine the predictors of metabolic syndrome (N = 354)

Variable	NCEP-ATP III Criteria		JIS Criteria	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex		0.336		0.505
Male (*Ref.)*	–	–	–	–
Female	1.42 (0.70–2.90)	0.336	1.25 (0.65–2.37)	0.505
Age	1.02 (0.98–1.05)	0.374	1.02 (0.99–1.06)	0.157
BMI	1.15 (1.08–1.22)	**0.000**	1.20 (1.13–1.27)	**0.000**
Duration on ART	1.00 (1.00–1.01)	0.781	1.00 (1.00–1.01)	0.493
ART therapy		**0.007**		**0.013**
TDF + 3TC + DTG (*Ref.*)	–	–	–	–
ABC + 3TC + DTG	2.74 (1.45–5.18)	**0.002**	2.50 (1.38–4.54)	**0.003**
ABC + 3TC + ATV/r	5.23 (1.01–27.08)	**0.049**	3.61 (0.66–19.83)	0.140
TDF + 3TC + ATV/r	1.13 (0.12–10.70)	0.916	0.66 (0.07–6.71)	0.727

ART antiretroviral therapy; *BMI* body mass index; *Ref.* reference category; *OR* odds ratio; *CI* confidence interval; *NCEP-ATP III* Third Report of the National Cholesterol Education Programme Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; *JIS* Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity; *TDF* tenofovir disoproxil fumarate; *3TC* lamivudine; *DTG* dolutegravir; *ABC* abacavir; *ATV/r* ritonavir-boosted atazanavir; bold values are significant at $p < 0.05$.

Predictors of the metabolic syndrome among participants

Results of binary logistic regression revealed that BMI and type of antiretroviral therapy were significant predictors ($p < 0.05$) of metabolic syndrome, using both the NCEP-ATP III and JIS criteria. The likelihood of having the syndrome increased with BMI (odds ratio [OR] = 1.15, 95% confidence interval [CI] = 1.08–1.22, $p<0.001$ vs OR = 1.20, 95% CI = 1.13–1.27, $p<0.001$ for the NCEP-ATP III and JIS criteria, respectively). Based on the NCEP-ATP III criteria, participants taking abacavir-lamivudine-dolutegravir (OR = 2.74, 95% CI = 1.45–5.18, p = 0.002) and abacavir-lamivudine-atazanavir/ritonavir (OR = 5.23, 95% CI = 1.01–27.08, p = 0.049) were more likely to have the syndrome compared to those taking tenofovir-lamivudine-dolutegravir. According to the JIS criteria, participants taking abacavir-lamivudine-dolutegravir were more likely to have the syndrome compared to those taking tenofovir-lamivudine-dolutegravir (OR = 2.50, 95% CI = 1.38–4.54, p = 0.003). (Table 3)

DISCUSSION

This present study aimed to determine the prevalence and risk factors of the metabolic syndrome among PLWH using antiretroviral medications at a referral hospital in Nigeria. The prevalence of metabolic syndrome in this study was 18.1% and 24.0%, according to the revised NCEP-ATP III and JIS definitions, respectively. Based on both definitions. BMI and the type of antiretroviral therapy the participants were using were significant predictors of metabolic syndrome.

The prevalence of metabolic syndrome obtained in the present study falls within the global prevalence of 16.7%–31.3% in PLWH based on various definitions.[21] Prevalence rates ranging from 12.7%–50.3% have been reported in other parts of Nigeria[13,14,22,23] and 19.2%–48.3% in other African countries.[12,24,25] The variations in the prevalence obtained in these studies may be attributed to differences in study design, sample sizes, demographic characteristics of participants, and the various criteria used to define metabolic syndrome.[26]

Out of all the components of the metabolic syndrome assessed, elevated blood pressure was the most common. About half of the participants had elevated blood pressure (≥130/85 mmHg). This is worrisome, as data suggest that both elevated and borderline blood pressure are associated with a significantly greater relative risk of acute myocardial infarction in PLWH compared to people without HIV.[27] This highlights the importance of implementing strategies for effectively managing and controlling hypertension, or elevated blood pressure, in this population. Although only a few participants in this study had previously been diagnosed with diabetes, evidence indicates that the number of components of the metabolic syndrome contributes to disease progression and risk in people who have developed diabetes.[5]

In this study, BMI was a significant predictor of metabolic syndrome among PLWH. Increasing BMI was associated with an increased likelihood of having metabolic syndrome. Similar findings have been reported among PLWH.[13,22] A recent study found that BMI is sufficient to predict diabetes or metabolic syndrome as reliably as more precise tests of body fat distribution in PLWH.[28] Although some antiretroviral therapies like tenofovir-lamivudine-dolutegravir have been associated with weight gain,[29] patients on such a regimen may be advised on appropriate management of modifiable factors linked to weight gain like a sedentary lifestyle/lack of physical activity, excessive intake of calories, inadequate sleep, stress, etc. Healthcare providers should educate PLWH on the need to adopt healthy lifestyles, which include healthy eating, increased physical activity, and stress management.

Antiretroviral therapy also predicted the odds of having metabolic syndrome in this study, irrespective of the criteria used. The odds of having metabolic syndrome were higher in participants taking abacavir-lamivudine-dolutegravir and those taking abacavir-lamivudine-atazanavir/ritonavir than in those taking tenofovir-lamivudine-dolutegravir. By contrast, Ayodele et al.[22] and Malindisa et al.[24] found no statistical difference between the use of a specific antiretroviral medication and metabolic syndrome among their participants. However, while the participants in the Ayodele et al. study were on older first-line antiretroviral regimens and none of them were using a PI-based regimen, the Malindisa et al. study compared tenofovir-lamivudine-dolutegravir regimen with older first-line regimens and PI-based regimens.

Our findings could be explained by several factors: PIs like atazanavir and ritonavir (used to 'boost' the antiretroviral activity of other PIs) are known to affect glucose metabolism causing hyperglycaemia, new-onset diabetes mellitus, or exacerbations of diabetes mellitus.[30] In addition to its effect on glucose metabolism, ritonavir can also cause dyslipidaemia and abnormal fat redistribution,[26,31-33] although the effect of ritonavir on plasma lipid levels is lower for atazanavir/ritonavir compared to lopinavir/ritonavir and fosamprenavir/ritonavir combinations.[34,35] Furthermore, although both abacavir and tenofovir are NRTIs, abacavir can cause hypertriglyceridaemia as well as abnormal redistribution and/or accumulation of body fat, whereas tenofovir has been found to have a favourable effect on lipids.[36,37] Further, although dolutegravir (an integrase strand transfer inhibitor) causes increases in cholesterol and triglycerides, these effects are minimal when compared with those of PI-based regimens.[38]

For the foregoing reasons, it may be beneficial to consider discontinuing the problematic antiretroviral regimen or single drug if safer and effective alternatives are available.[39] When substituting with an alternative regimen or drug, however, other potential factors that could contribute to the problem (e.g., lifestyle, heredity) should be evaluated. Additionally, the possible effect on virologic suppression and toxicities of the new agent(s), adherence, clinical history, antiretroviral therapy history, and virologic responses to previous antiretroviral therapies should be considered.[16,31]

Implications of findings

The findings of this study have revealed that metabolic syndrome is prevalent among PLWH in the study setting. Routine screening for the syndrome among PLWH is thus important to identify the syndrome early and initiate prompt management. In addition, information on lifestyle such as physical activity, diet (including intake of fruits and vegetables), alcohol consumption, family history of diabetes, hypertension, etc. should be obtained from PLWH on every clinic appointment. This is particularly important for at-risk populations like those who are overweight or obese, have a history of any of the metabolic syndrome components, or are on an abacavir-based or second-line antiretroviral regimen. This should be followed up with patient education as deemed appropriate.

Strengths and limitations

Since the introduction of the dolutegravir-based first-line antiretroviral regimen, this is the first study that, to the best of our knowledge, has examined the relationship between specific antiretroviral therapy and metabolic syndrome among PLWH in southern Nigeria. Furthermore, the study was conducted on a representative sample in a region of the country with a high prevalence of HIV infection.[19,20] The study, however, has some limitations. First, a cross-sectional study design was adopted; as a result, causality cannot be ascertained from the findings. Second, the study was conducted in one setting, which limits the generalisability of the findings. Nevertheless, the setting is the major referral hospital in a state with a high HIV prevalence in the country. Third, several other established risk factors for metabolic syndrome, such as physical activity, diet, smoking status, family history of a metabolic disorder, etc., were not assessed in our study; hence, confounding from these risk factors may have influenced our results.

CONCLUSION

Metabolic syndrome appears to be common among the PLWH surveyed. Education on the adoption and maintenance of healthy lifestyles should be promoted among PLWH. In addition, careful selection of antiretroviral therapy is crucial for PLWH in order to reduce the incidence of metabolic syndrome and their risk of cardiovascular events and mortality. Future research efforts could utilise a prospective design involving a larger sample size from various settings in order to gain a better understanding of the prevalence and determinants of metabolic syndrome in PLWH.

Authors' contributions

Conceptualisation: IJ; Methodology: IJ, EN, MA, EU, IA, AE, IE; Formal analysis and investigation: IJ, MA; Writing - original draft preparation: IJ; Writing - review and editing: IJ, EN, MA, EU, IA, AE, IE; Funding acquisition: IJ; Resources: IA, AE; Project administration: IJ.

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