Original Article

Prevalence and Correlates of Metabolic Syndrome in Patients Receiving Highly Active Antiretroviral Therapy Attending Infectious Disease Clinic in a Southwest Tertiary Health Institution in Nigeria

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Abstract

Background: The introduction of HAART has led to significant decline in morbidity and mortality in HIV/AIDS patient however not without the emergence of a number of metabolic derangements. **Materials and Methods:** The study adopted cross sectional design carried involved one hundred and fifty participants who fulfilled the inclusion criteria. 10mls of blood samples was collected after overnight fasting, distributed into appropriate specimen bottles for fasting blood glucose, CD4 count, viral loads and lipids profile assays. **Results:** There mean age was 41.94 years with female preponderance and male to female ratio of 1:3.81. The common ART used among subjects was tenofovir/lamivudine/dolutegravir (98.4%). The log mean CD4 count was 5.58. The prevalence of abdominal obesity among subjects was 42.4% according to National Cholesterol Education Program for Adult treatment Panel III (NCEP-ATP III), and a higher prevalence of 56.8% according to International Diabetes Foundation/joint interim statement (IDF/JIS) criteria. High fasting glucose was evident in 24.8% ($n = 31$), hypertriglyceridemia in 12.8%, majority (76%) had low high-density lipoprotein and high blood pressure in more than one third (43.2%) of the population. The prevalence of metabolic syndrome among subjects ranged between 35.2% and 43.2% according to the NCEP-ATP III, IDF, and JIS criteria. **Conclusion:** The prevalence of metabolic complications of HAART in patients with HIV infection observed in this study is high despite improvements in morbidity and mortality conferred by immune reconstitution. The long-term effects of these metabolic complications indicate the need for concern and active preventive measures. These findings call for an integrated management strategy.

Keywords: Cardiovascular disease, CD4 count, diabetes mellitus, highly active antiretroviral therapy, HIV/AIDS, metabolic syndrome, viral loads

Received on: 23-10-21 **Accepted on:** 25-12-21 **Published on:** ***

Introduction

The introduction of highly active antiretroviral therapy (HAART) in the mid 1990's, has led to dramatic decline in immunodeficiency-related events among HIV-infected individuals,[1-3] life-expectancy increased, which also exposed them to the effects of aging, including the influence of some environmental risk factors contributing to the occurrence of co-morbidities.[4,5]

HIV/AIDS, has remained a public health concern in Sub-Saharan Africa, where an estimated 25.8 million adults and children are infected.[6] HIV patients have a large variety of physiological alterations at every level of the disease, in synergy with related pathologies give rise to different nutritional problems.[7]

Access this article online

Quick Response Code:

Website: www.atpjournal.org

DOI: 10.4103/atp.atp_18_21

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How to cite this article: Salawu AA, Kareem RA, Oke EO, Oloyede TW, Ojedokun SA, Oreagba K. Prevalence and correlates of metabolic syndrome in patients receiving highly active antiretroviral therapy attending infectious disease clinic in a southwest tertiary health institution in Nigeria. Ann Trop Pathol 2022;XX:XX-XX.

Since the introduction of HAART, the decline in morbidity and mortality has been clouded by the emergence of a number of metabolic derangements.[8-10] These disorders include dyslipidemia, insulin resistance, abnormalities of glucose metabolism, and changes in fat distribution.[9,10] Hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), insulin resistance, and increased waist circumference can occur simultaneously in HIV infection and are reminiscent of metabolic syndrome in the general population, which increases the risk of cardiovascular disease.[11]

Recent studies of HIV-infected persons have revealed a high prevalence of metabolic syndrome among patients receiving HAART.[12-14] HAART itself in a high proportion of patients causes metabolic disorders characterized by lipodystrophy, dyslipidaemia and insulin resistance, which may be associated with an increase in coronary artery disease and stroke.[15] The prevention of this cardiometabolic morbidity by using antiretroviral (ARV) drugs with a low metabolic toxicity and the treatment after its early detection are the current control strategies.[16]

However, this study is set to identify any association between the use HAART and development of metabolic disorders.

Materials and Methods

Settings and design

This is a cross sectional study carried out at the Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital Ogbomoso among subjects attending infectious disease clinic and presently on ARV treatment. One hundred and twenty-five subjects were randomly selected and questionnaires were administered after signing the writing informed consent.

The inclusion criteria were all adult with confirmatory diagnosis of human immunodeficiency virus (HIV) and currently receiving HAART at the clinic. Those confirmed and not yet on HAART and all subjects on HAART but presently have on-going acute illness or chronic liver or kidney diseases are excluded. All patients on supplement that can affect lipid metabolism were also excluded from the study.

Sample collection, storage and laboratory analysis

Under aseptic technique, 10mls of blood samples was collected from the patients after overnight fasting via the antecubital vein. 3mls was put inside fluoride oxalate bottles for fasting blood glucose (FBG), 3.5 ml into ethylenediaminetetraacetic acid sample bottles for CD4 count and viral loads, and the remaining 3.5mls into serum extractor plain containers for lipids profile assays. The plasma obtained in fluoride oxalate bottle was used for blood glucose estimation and this was done on each clinic days. The blood samples in plain container were centrifuged at 3500 × g for 10 min to obtain serum and frozen at − 40°C till analysis was done. Plasma and serum from both subjects and controls were analyzed in batches using standards and controls from manufacturers of reagent kits for all the biochemical parameters. Serum total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), triglycerol and plasma glucose were analyzed using Roche Cobas c111 automatic analyzer at the Metabolic Research Laboratory of LAUTECH Teaching Hospital Ogbomoso.

Statistical analysis

Data entry was done and analyzed using Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Software Group, Chicago, IL, USA). Categorical variables were expressed in percentages and continuous variables were summarized using mean ± standard deviation. Relationships between categorical variables were analyzed using Chi-square, Fisher's test and likelihood ratio test where appropriate. Differences in means between continuous variables were analyzed using *t*-test.

Results

Socio-demographic profile of subjects

Table 1 shows the socio demographic profile of subjects in the study population. Subjects aged between 16 and 73 years, and majority (63.2%) were between 30 and 49 years, and a mean age of 41.94 ± 11.00. There was female preponderance with a male to female ratio of 1:3.81 (male: 20.8%, female: 79.2%). The common ART used among subjects was tenofovir/lamivudine/dolutegravir (98.4%). CD4 count (cells/mm^3) varied largely among respondents with a minimum of 19 (cells/mm^3), maximum of 1910 (cells/mm^3) and a mean of 382.28 ± 332.71 (cells/mm^3). The log mean CD4 count was 5.58 ± 0.91 (cells/mm^3) [Table 1].

Anthropometric and biochemical characteristics of the study population

Table 2 depicts the anthropometric and biomedical characteristics of subjects in the study population. The mean

Table 1: Sociodemographic profile of subjects

Variables	Frequency, *n* (%)
Sex	
Male	26 (20.8)
Female	99 (79.2)
Age (years)	
≤29	17 (13.6)
30-49	79 (63.2)
50-69	25 (20.0)
≥70	3 (2.4)
ART	
TLD	123 (98.4)
Atazanavir/ritonavir	2 (1.6)
CD4 count (cell/mm^3)	
Minimum	19
Maximum	1910
Mean±SD	382.28±332.71
Mean±SD (Log CD4)	5.58±0.911

Frequency: Number of subjects, mean age: 41.94±11.00, mean CD4 count. SD: Standard deviation, ART: Antiretroviral therapy, TLD: Tenofovir/Lamivudine/Dolutegravir

weight was 68.3 ± 17.1 (kg), a mean height of 1.60 ± 0.10 (m) and a mean BMI of 26.74 ± 5.99 (kg/m^2). The mean abdominal circumference was 87.61 ± 13.37, mean hip circumference of 98.66 ± 11.75. The mean systolic blood pressure among subjects was 125.89 ± 18.07 (mmHg), and mean diastolic blood pressure of 76.92 ± 11.30 (mmHg). The mean FBG was 4.79 ± 1.79 (mm/mol), TG had a mean of 0.87 ± 0.61 (mm/mol) and HDL-C had a mean of 1.03 ± 0.36 (mm/mol).

Risk factors of metabolic syndrome among subjects in the study population

The risk factors of metabolic syndrome among subjects are shown in Table 3 according to National Cholesterol Education Program for Adult treatment Panel III (NCEP-ATP III), International Diabetes Foundation (IDF), and joint interim statement (JIS) criteria. All risk factors except abdominal obesity have the same cut off values across the three criteria. The prevalence of abdominal obesity among subjects was 42.4% according to NCEP-ATP III, and a higher prevalence of 56.8% according to IDF/JIS criteria. High fasting glucose was evident in 24.8% (n = 31), hypertriglyceridemia in 12.8%, majority (76%) had low HDL and high blood pressure in more than one third (43.2%) of the population.

Table 2: Anthropometric and biochemical parameters among subjects in the study population

Parameters	Mean ± SD
Weight (kg)	68.3±17.1
Height (m)	1.60±0.10
BMI (kg/m^2)	26.74±5.99
Abdominal circumference	87.61±13.37
Hip circumference	98.66±11.75
SBP (mmHg)	125.89±18.07
DBP (mmHg)	76.92±11.30
Pulse rate	77.67±13.16
FBG (mm/Mol)	4.79±1.79
TG (mm/Mol)	0.87±0.61
HDL-C (mm/Mol)	1.03±0.36

Hypertriglyceridemia in 12.8%, majority (76%) had low HDL and high blood pressure in more than one third (43.2%) of the population. HDL-C: High density lipoprotein cholesterol, SD: Standard deviation, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, TG: Triglycerides

Table 3: Risk factors of metabolic syndrome among subjects in the study population

Risk factors	NCEP-ATP III, *n* (%)	IDF, *n* (%)	JIS, *n* (%)
Abdominal obesity	53 (42.4)	71 (56.8)	71 (56.8)
High fasting glucose	31 (24.8)	31 (24.8)	31 (24.8)
Hypertriglyceridemia	16 (12.8)	16 (12.8)	16 (12.8)
Low HDL_C	95 (76.0)	95 (76.0)	95 (76.0)
High blood pressure	54 (43.2)	54 (43.2)	54 (43.2)

NCEP-ATP III: National cholesterol education program for adult treatment Panel III Guidelines, IDF: International Diabetes Foundation, JIS: Joint interim statement, HDL-C: High density lipoprotein cholesterol

Prevalence of metabolic syndrome among subjects in the study population

The prevalence of metabolic syndrome among subjects ranged between 35.2% and 43.2% according to the NCEP-ATP III, IDF, and JIS criteria [Figure 1]. The prevalence of metabolic syndrome was 35.2% according to NCEP-ATP III criteria, 36.8% according to IDF criteria and a prevalence of 43.2% was obtained using the JIS criteria.

Discussion

Metabolic syndrome prevalence in this cohort of HIV-infected patients was 35.2-43.2%. There was a 96% agreement in patient classification between NCEP-ATP III and IDF criteria; 35.2% and 36.8% respectively. The prevalence of metabolic syndrome found in this study was higher to that from a Spanish study,[14] which showed a rate of 17% using ATPIII criteria.

Metabolic syndrome was associated with increased prevalence of abdominal obesity among subjects. The prevalence of abdominal obesity was 42.4%–56.8% with a higher prevalence of 56.8% recorded according to IDF/JIS criteria. High fasting glucose was evident in 24.8%, hypertriglyceridemia in 12.8%, where majority (76%) had low HDL and high blood pressure in more than one third (43.2%) of the population.

CD4 count (cells/mm^3) varied largely with a mean of 382.28 ± 332.71 (cells/mm^3). Among HIV-related factors, although a higher CD4 cell count was an independent predictor of the development of metabolic syndrome, a higher BMI accounted for a substantial part of the CD4-attributable risk.

Other studies have found a lower CD4 cell count to be associated with metabolic syndrome or increased cardiovascular risk.[17-20] However, there was no significant difference in the mean CD4 count of subjects by metabolic syndrome consistently for all the three criteria.

Several pathophysiologic models have been proposed to explain the development of dyslipidaemia in HIV-infected patients, involving several proposed interactions between the virus, ARV therapies, and host factors. In one model, protease inhibitors, through various proposed actions, cause increased

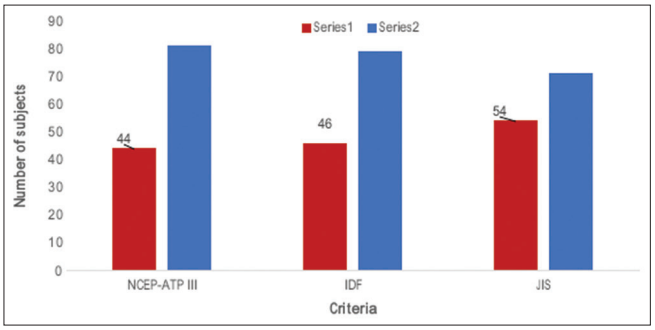

Figure 1: Prevalence of Metabolic Syndrome according to NCEP-ATP III, IDF and JIS criteria. NCEP-ATP III: National Cholesterol Education Program for Adult treatment Panel III Guidelines, IDF: International Diabetes Foundation, JIS: Joint interim statement

activity of sterol regulatory element-binding protein (SREBP), which alters adipocyte differentiation (contributing to lipodystrophy) and reduces leptin levels. In hepatocytes, SREBP induces lipogenic genes, which leads to increase hepatic very-low-density lipoprotein production.[17,18,21,22] The increased lipid levels and reduced leptin levels, in turn, cause insulin resistance, which further activates SREBP, thus perpetuating the cycle.[23] However, majority of subjects in this study were on NRTIs, which are associated with fat loss; an improvement in lipoatroph.[24]

A direct atherogenic effect of HIV infection itself or ARV drugs is unlikely. Epidemiological studies suggested an increased risk for coronary artery disease in HIV infected persons; nevertheless, only long term follow, confirm this statement. Despite these uncertainties, it is reasonable to identify and manage cardiovascular risks of HIV infected patients.[25]

Mondal *et al*. demonstrated that the oxidative stress can disrupt endothelial homeostasis by dysregulating the balance between pro and anti atherogenic factors. The chronic exposure to HAART results in endothelial oxidative stress and activation of mononuclear cells recruitment, an early event in atherosclerosis.[24]

The lipid profiles of HIV positive patients are characterized by low levels of HDL as observed in this study and high levels of both LDL-C and TC; this type of lipid profile predisposes patients to atherogenesis. Some studies have shown that the incidence of cardiovascular events in patients with HIV infection who are on HAART is higher than that in the general population.[26,27]

The prevalence of metabolic syndrome found in this cohort was increased compared to other reported as 14% to 25%.[28-31] Metabolic syndrome prevalence was either similar to[30,31] or greater[29] than that of control groups. Metabolic syndrome in HIV-infected HAART recipients was associated with greater insulin resistance and lipid disturbances, and a pro-inflammatory milieu with higher C-reactive protein levels and lower adiponectin levels.[28] Metabolic syndrome presence was associated with higher BMI, higher viral load, and use of ritonavir-boosted lopinavir and didanosine.[30] Interestingly, two studies suggest specific anthropometric limitations to the metabolic syndrome definitions promulgated when applied to HIV-infected HAART recipients.[26] Waist circumferences were lower in HIV-infected HAART recipients compared with the uninfected population despite similar prevalence rates for metabolic syndrome,[30] and 50% of HIV-infected HAART recipients met non-anthropometric criteria for metabolic syndrome, but this reduced to 17% when waist-based anthropometric cutoffs were applied.[28] As such, metabolic syndrome definitions may not be sufficiently sensitive for HIV-infected HAART recipients. Two studies have reported the incidence of metabolic syndrome after HAART initiation. One study found the prevalence of metabolic syndrome increased from 16% to 25% over 48 weeks, with an incidence rate of 14/100 patient years.[30] A recent 3 years study following HAART initiation in treatment-naïve patients reported a baseline prevalence of metabolic syndrome of 9% and an incidence of 12/100 patient years.[31] The relative risk of developing diabetes was increased 4-fold in those with metabolic syndrome prior to HAART commencement.[31] In those developing metabolic syndrome on HAART, the risk of diabetes was increased 4-to 5-fold and cardiovascular disease 3-fold.[31]

In HIV infected patients, the impact of ARV drugs in the pathogenesis of metabolic syndrome is sometimes questioned in studies reporting no difference in infected patients receiving HAART compared to treatment-naive patients.[32,33] Similarly, the incidence of metabolic syndrome doesn't differ in HIV-infected patients compared to non-infected patients or the general population.[21,24,29,34,35] Despite these controversies, and because HIV infection is a cardiovascular risk factor, metabolic syndrome should be more prevalent in HIV-infected patients.

In accordance with our observations, low HDL-cholesterol was the main biological disorder of metabolic syndrome in these group of patients.[21,36,37] Other authors report high triglycerides.[34] In addition to abdominal obesity, low HDL-cholesterol plus abnormal blood pressure was the common phenotype of metabolic syndrome in our patients. This differs from studies suggesting the frequency of the phenotype high triglycerides plus abnormal blood glucose in patients receiving HAART compared to treatment-naive patients.[33] Other studies report the profiles of abnormal blood pressure plus high triglycerides and low HDL-cholesterol in treatment-naive patients[38] or the profiles of low HDL-cholesterol plus high triglycerides and a low incidence of abnormal blood glucose in HIV-infected patients compared to non-infected one.[29] Changes in clinical and biological standards depending on diagnosis criteria of the metabolic syndrome as well as the metabolic side effects of each HAART regimen could partly explain these differences.

Conclusion

Though the benefits of HAART use are overwhelmingly greater than possible MetS and CVD risks, close management of those patients is called for, especially due to the fact that general population risk factors now overlap with specific ones in this population, even though the former are usually more prominent than the latter.

Thus, MetS in HIV populations ought to be closely monitored and controlled by programmatic and comprehensive public measures. These findings call for an integrated management strategy.

Finally, comprehensive educational measures are needed and further research is instrumental to assess the barriers to implement preconized interventions and to achieving recommended treatment goals that are singular to the HIV-population.

Acknowledgement

This is to appreciate everyone who have contibuted in one way or the order towards the success of this research work starting from

proposal approval, sample colletion, data input and analysis, proof reading ad immerse contributions from every co-author.

A very big thanks to you all.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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