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CARDIAC TROPONIN AND CREATINE KINASE IN HUMAN IMMUNODEFICIENCY VIRUS INFECTED PATIENTS ON ANTIRETROVIRAL DRUGS

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ABSTRACT

People living with HIV are living a longer and productive life due to the effective viral suppression by highly active anti retroviral therapy (HAART). They are therefore exposed to metabolic syndromes associated with aging and lifestyle. This study was therefore designed to access the contribution of HAART to cardiovascular diseases in HIV patients. Patients on HAART were randomly selected (100) from the study population. Age and sex matched controls were treatment naïve HIV positive patients (50) and blood donors (50). Fasting blood samples were taken for cardiac troponin, cardiac creatine kinase, glucose and lipid profile. The fasting blood glucose was significantly higher in HIV patients ($p < 0.0001$) than in HIV negative blood donors. The lipid profile showed that triglycerides (TG) and very low density lipoprotein (VLDL) were significantly higher in HIV patients while the total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were lower compared to blood donors. The introduction of HAART increased the low density lipoprotein cholesterol (LDL) and TC but reduced the HDL further. There were no significant differences in the levels of troponin 1 and creatine kinase among the groups. There was tendency to reduced insulin sensitivity with raised levels of triglyceride and VLDL but low HDL. Therefore cardiovascular risk factors exist though the cardiac markers were not significantly increased in this study. People living with HIV

should be counseled to avoid cardiovascular risk factors and to have these parameters monitored regularly.

KEYWORDS: Human immunodeficiency virus, dyslipidemia, insulin sensitivity, cardiovascular disease.

INTRODUCTION

Persistent HIV infection is a state of chronic inflammation and oxidative stress even in the absence of opportunistic infections.[1,2] These are mediated by shed viral particles like gp120, trans activator of transcription (tat), nef and viral protein R (vpr) that interact with chemokine receptors on macrophages among other cells[1,2] Pro-inflammatory cytokines like tumor necrotic factor, interleukin, interferon α and λ are consequently released via activation of the nuclear factor kappa/beta[1,2,3,4]

Macrophages under the influence of inflammatory signals marginate and migrate to the sub endothelium where they differentiate into foam cells due to reduced reversed lipid tissue movement mostly by high density lipoproteins[5] Accumulation, oxidative stress and apoptosis of these foam cells lead to deposits of atheroma and intimal thickening. Generalized arteriosclerosis favored by these changes is a risk factor to cardiovascular accidents and sudden death.[5]

Increase in visceral fat as seen in HIV patients on protease inhibitors is associated with reduced adiponectin, an adipocyte hormone, that improves hepatic sensitivity, increase fuel oxidation and decrease vascular inflammation.[6,7,8] Insulin drives triglycerides and glucose into tissue for the production of energy. It is therefore expected that increase in visceral fat and chronic inflammation will reduce fat and glucose utilization with development of metabolic syndrome.[9]

All of the protease inhibitors (PIs) except atazanavir have been associated with lipodystrophy, elevations of low density lipoprotein (LDL), total cholesterol (TC) and triglyceride (TGs) with a decrease in high density lipoprotein cholesterol (HDLC).[10,11,12,13,14] PIs suppress the breakdown of transcription factors such as nuclear sterol regulatory element binding proteins (nSREBPs). The accumulation of nSREBP in the liver causes increased cholesterol, increase fatty acids synthesis and insulin resistance.[15,16,17] PIs cause inhibition of cytochrome P450 and inhibition of the breakdown of apolipoprotein B with increase in LDL-

C in circulation. They also prevent adipocyte differentiation with increased adipocyte apoptosis, leading to hyperlipidemia and reduction in liver chylomiron clearance.[16,18]

The nucleoside reverse transcriptase inhibitors (NRTIs) especially stavudine and didanosine are associated with hepatic steatosis related to mitochondrial toxicity and increase in TG, LDL and TC. Among non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz is more likely to cause hyperlipidemia than nevirapine.

The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III defines metabolic syndrome as presence of at least 3 of the following risk factors: waist circumference >88 cm [women] or >102 cm [men]; blood pressure >130/85 mm Hg or drug treatment for hypertension; triglycerides > 150 mg/ dL; fasting glucose >100 mg/dL; and HDL cholesterol <50 mg/dL in women or <40 mg/dL in men.[19]

The INITIO study showed a rate of 12 per 100 patient's years for the development of metabolic syndrome during 3 years of follow-up of patients on NNRTI or PI-based therapy.[20] Another study found that the incidence of metabolic syndrome was 14% in HIV-infected adults and was associated with increased levels of leptin and C-reactive protein (CRP) and decreased levels of adiponectin.[21] A database of the Kaiser Permanente health care plan showed an increased rate of heart attack and coronary artery disease in people with HIV compared with adults without HIV in an age-matched analysis, but there was no relationship to the type of treatment.[22] Studies have also shown that HIV is associated with cardiovascular manifestations, cardiovascular risk factors and that the relative risk of myocardiac infarct was 1.4-fold greater in men and 3-fold greater in women.[23,24,25,26,27]

This study sought to determine if there were subclinical myocardial damage in these patients using cardiac troponin I which has high specificity for cardiac injuries even in the presence of renal failure and myocardial isoform creatine kinase (CK-MB).[28,29]

MATERIALS AND METHODS

Study Design

This study was carried out at the adult anti retroviral therapy (ART) clinic of the Haematology department, Lagos State University Teaching Hospital, Ikeja. Ethical approval was obtained from the Hospital's Health Research Ethical Committee (LASUTH-HREC-

LREC/10/06/659). Informed consent was obtained in writing after the purpose and demands of the study had been explained to the participants.

This was a cross-sectional study. The study population was H.I.V Positive patients, both males and females regularly attending Adult ART Clinic and the controls were HIV negative blood donors. The sample frame was a list of 1,980 patients who have been on ART for more than 3 years. This was generated from the pharmacy computer. The sample size as calculated using the technique for cross-sectional studies with a 12% prevalence of metabolic syndrome in HIV was 188.[20] A list of one hundred and eighty eight patients was therefore randomly generated from the sample frame using Microsoft Excel with the command Randbetween and sort. During the period of study, which was 3 months from March 2016 to May 2016, 100 of the 188 treatment experienced randomized participants (group A) were eligible and gave consent to participate in the study. Age and sex matched treatment naïve HIV positive participants (50) were recruited at time of registration (group B). Consenting blood donor (50) who were HIV negative (group C) were recruited as controls. Group B and C were recruited using convenience and purposeful sampling since the sample population of each group was infinite and the sample size was based on 3-4% prevalence of HIV in Nigeria. Eligibility criteria included consenting participants with previously documented HIV infection who have been on ART for at least three years and stable HIV seropositive subjects who are treatment naïve. Age of participants was restricted to between 18 and 45 years to avoid the influence of age. Participants with the following conditions were excluded from the study: renal impairment; chronic hepatitis by screening for hepatitis B and C; history of tuberculosis or chronic inflammatory disorders or of diabetes. Other exclusion criteria used included obesity, history of smoking, heavy alcohol consumption and use of other drugs that may affect the liver or the heart (acetaminophen, amiodarone, chlorpromazine, diclofenac, erythromycin, fluconazole).[31] A structured questionnaire and data from case notes were used to determine the demographic features of participants and suitability for participation.

Sample Collection And Processing

10ml of whole blood was collected from the subjects directly into 3 vacutainers (EDTA, Fluoride oxalate and Plain) after an overnight fast of 12-14 hours. Samples in the EDTA containers were processed for CD4 cell count and rapid screening test for hepatitis B and C within two hours of collection. CD4 absolute count was done using Flow Cytometric technique, with Partec Cyflow Counter 2.

Plasma was separated from the sample in the Fluoride oxalate container immediately and stored at -20^{o}C for blood glucose analysis. Serum was separated from the samples in the plain containers immediately after clot retraction and aliquots stored at -80°C until analysis. The serum was used for cardiac markers and lipid profile assays.

TC, TG, HDL, LDL and VLDL) and Creatine Kinase CK-MB were estimated using automated procedures with Cobas C111 manufactured by Roche. ELISA technique was used for Cardiac Troponin-1 assay with Stat Fax 4700 microplate reader. The ELISA kit used in this study was a product of Accu Bind ELISA Microwells (Troponin-1 (cTnl) Test System. Product code: 3825-300). Manufacturer's quality conditions and validity criteria were duly observed.

Statistical Analysis

Data obtained from the questionnaire as well as those from quantitative analysis of the analytes were entered into Microsoft excel 2007 software and data were analyzed using GraphPad In Stat 3 program. The means were compared using unpaired t-test, or Mann-whitney test for non parametric data. Comparison of the three groups was done using ANOVA with Post Hoc test. P value less than 0.5 was considered significant.

RESULTS

The socio-demographic and clinical characteristics of the participants *are* summarized in Table 1. The mean age of all participants was 34.6yrs ± 7.0 and there was no significant difference in the mean age, comparing groups (A vs B) and (B vs C), ($P > 0.05$); but there was significant difference in mean age of group A vs group C ($P < 0.001$). There was no statistically significant difference in sex distribution within the groups ($P = 0.196$). There was no statistically significant difference in the mean BMI of the three groups ($P = 0.402$). Both Systolic and Diastolic Blood Pressures were within normal reference range. There was no significant difference in CD4 count of treatment experienced and the treatment-naïve groups ($P > 0.05$).

Table 1: Mean Age, Gender distribution, Body Mass Index, Blood Pressure (BP) and CD4 count of Respondents.

	HAART (n=100)	HAART-naive (n=50)	CONTROL (n=50)	P-value
Male	24	18	18	
Female	76	32	32	0.196
AGE (Years):	37.1 ± 5.5	34.5 ± 7.0	30.7 ± 8.4	< 0.0001*
BMI	25.5 ± 4.7	24.5 ± 4.6	25.3 ± 3.8	0.402
BP-Systolic	121.2 ± 13.4	122.9 ± 15.0	118.4 ± 11.0	
B P-Diastolic	69.1 ± 14.3	71.8 ± 11.6	75.0 ± 12.3	
CD4 count (cells/ul)	464.8 ± 192.9	421.3 ± 354.2	885.8 ±261.1	< 0.0001*

Statistically significant @ P < 0.05. HAART- highly active antiretroviral treatment.

Table 2 summarizes the clinical stage of HIV positive participants. Those in HIV clinical stage I at the time of diagnosis of the HIV infection were 115(76.7%), 27(18%) were in stage II, while 8(5.3%) were in stage III of the infection.

Table 2: Clinical stage of HIV Infection at time of Diagnosis.

	STAGE I	STAGE II	STAGE III	TOTAL
HAART-Experienced	80%	15%	5%	100%
HAART-Naïve	70%	24%	6%	100%
TOTAL (%)	115(76.7%)	27(18.0%)	8(5.3%)	150(100%)

Stage I: Asymptomatic stage; Stage II: Mild Symptomatic stage; Stage III: Moderately Symptomatic stage (WHO, 2005).

Table 3 shows the frequency of usage of each drug by the participants. Lamivudine was used by all participants. 65.1% were on Nevirapin, 60% on Zidovudine and 39.5% on Tenofovir. Abacavir and Lopinavir (4.7% each) were the least used by the participants. Atazanavir was not used by any of the participants.

Table 3: Frequency of usage of each drug.

Class of Drug	Name of Drug	Frequency (%)
NRTIs	Lamivudine	86(100%)
	Zidovudine	49(60%)
	Abacavir	4(4.7%)
	Tenofovir	34(39.5%)
NNRTIs	Nevirapin	56(65.1%)
	Efaverence	27(31.4%)
PIs	Lopinavir	4(4.7%)
	Atazanavir	0(0%)

The mean values of both Troponin-1 and CK-MB in the three groups were within the normal reference ranges. There was no statistically significant difference in the three groups. Troponin-1 (P=0.29300); CK-MB (P=0.40 α43). See table 4.

Table 4: Mean Concentration of Troponin-1 and Creatine Kinase-MB in serum.

	HAART (n=100)	HAART-naive (n=50)	CONTROL (n=50)	P-value
Troponin-1 (ng/ml)	0.15 ± 0.3	0.14 ± 0.1	0 11 ± 0.1	0.2930
CK-MB (U/L)	9.34 ± 10.4	8.72 ± 8.1	6 62 ± 4.1	0.4043

Reference values: Troponin-1: Adult < 1.3ng/ml; CK-MB: Healthy people < 25U/L
Statistical significance: P < 0.05.

Table 5 summarizes the lipid profile of the three groups. The lipid fractions were within the reference range in all the groups. In HAART naïve patients, TC, HDL and LDL were significantly lower than that of blood donors ($p< 0.05$) while triglyceride and VLDL were higher ($p < 0.001$). In patients on HAART, the LDL, VLDL and TG were significantly raised ($p = 0.002$) compared to blood donors but HDL and TC were significantly reduced.

Table 5: Mean Concentration of Lipid Profile of subjects in serum.

	HAART (n=100)	HAART-naïve (n=50)	CONTROL (n=50)	P-value
Total Cholesterol (mmol/L)	3.20 ± 0.8	2.89 ± 0.7	3.57 ± 1.0	0.0005*
Triglyceride (mmol/L)	1.30 ± 0.6	1.45 ± 0.7	0.98 ± 0.7	< 0.0001*
HDL-C (mmol/L)	1.56 ± 0.5	1.78 ± 0.5	1.99 ± 0.5	< 0.0001*
LDL-C (mmol/L)	1.42 ± 0.8	0.83 ± 0.5	1.38 ± 0.9	0.002*
VLDL-C (mmol/L)	0.26 ± 0.1	0.29 ± 0.1	0.20 ± 0.1	0.001*

Reference values: TCHOL: < 5.2 mmol/L; Triglyceride: < 2.3 mmol/L; HDL-C: > 1.45 mmol/L); LDL-C: < 3.36 mmol/L). *Statistically significant @ P < 0.05.

The mean FBS was significantly higher in group B (5.57mmol/L ± 1.3) compared to group C (5.05mmol/L ± 0.9) (P < 0.001), and in group A (5.22mmol/L ± 0.8) compared to group C (P < 0.01); but there was no statistically significant difference in FBS between group A and group B (P > 0.05). See table 6.

Table 6: Mean Concentration of Fasting Blood Sugar (FBS).

	HAART (n=100)	HAART-naive (n=50)	CONTROL (n=50)	P-value
FBS (mmol/L)	5.22 ± 0.8	5.57 ± 1.3	5.05 ± 1.9	< 0.0001*

Reference values: FBS: (3.9 – 6.1) mmol/L; *Statistically significant @ P < 0.05

When the means of values obtained in participants on a particular drug were compared to values obtained if the drug was not in the treatment, there were no statistically significant differences. Tables 7 shows the p values.

Table 7: P – VALUES OF SUBJECTS ON SPECIFIC HAART AND OFF.

Name of Drug	GLUCOSE	CD4	VLDL	LDL	HDL
Zidovudine	0.39	0.37	0.84	0.79	0.81
Abacavir	0.77	0.62	0.44	0.61	0.40
Tenofovir	0.63	0.17	0.82	0.78	0.62
Efaverence	0.96	0.58	0.66	0.35	0.93
Nevirapin	0.95	0.58	0.66	0.35	0.35

DISCUSSIONS

There was no significant difference in sex distribution among the groups, though there were more females in the study population, which is a reflection of the proportion of females attending the adult ART clinic. Participants in group A had mean age that is significantly higher than the mean age of the control group C ($P < 0.0001$) but there was no significant difference in body mass index (BMI). Also, there was no evidence suggestive of high blood pressure in any of the groups. The risk factors of metabolic disorder are increased age, higher BMI, hypertension and diabetes.[30] Therefore, the only confounder is age in this study but limiting the age of participants should reduce this disadvantage. The drugs implicated in metabolic disorders were rarely used, participants with known history of metabolic disorders were excluded, 80% of the subjects were asymptomatic in this study and dietician/nutritionists were involved in the team managing HIV positive patients. These may account for the normal lipid profile and fasting blood sugar.

In this study, TG, VLDL were higher in HIV patients while the TC and HDL were lower compared to blood donors but the introduction of HAART increased the LDL and TC while it reduced the HDL further ($p < 0.002$ in all). This is similar to findings by Triant et al (2007) and Grinspoon et al (2008), which showed that HIV infection is associated with decreased HDL-C.[26,27] In Nigeria, work done by Ogundahunsi et al (2008) showed that TC and LDL-C were significantly raised, while HDL-C was reduced in those on ART compared to ART-naïve subjects.[31] Findings from other studies also showed that Protease Inhibitors (PIs) like lopinavir and tenofovir were associated with higher TC and LDL, and a lower HDL-C.[32,33,34,35] The increase in LDL-C and reduced HDL-C in the presence of inflammation and oxidative stress will increase the risk of cardiovascular lesions.[1,2,5]

The Fasting Blood Sugar (FBS) was significantly raised in HIV positive subjects irrespective of ART than in the control subjects ($p< 0.0001$). The FBS in ART-experienced subjects was less compared to ART-naïve subjects, though not statistically significant. This implies that ART may not cause added glucose metabolic disorder in HIV positive patients on long term basis. This is similar to the work of Basil et al, (2016), where HAART-naïve subjects tend to have higher two hour post-prandial (2HPP) blood sugar than HAART-experienced subjects.[36] The chronic inflammation associated with HIV infection have been shown to cause insulin resistance and therefore raise glucose intolerance in HIV positive patients.[37,38] Studies have shown that mitochondrial toxicity by NRTIs, especially stavudine can reduce

insulin sensitivity and that protease inhibitors have capacity to induce insulin resistance.[38,39] In this study, stavudine was not used and PIs were sparingly used. Therefore inflammatory changes appear to account for most of the differences observed.

Troponin-1 and creatine kinase-mb (CK-MB) values were within normal range in the three groups ($p>0.29$ and 0.40 respectively). However, the values, though not statistically significant, were raised in ART-experienced HIV positive subjects than in ART-naïve subjects and the values were lowest in the HIV negative control group. This is similar to the work done by Robert A et al (2014), in which there was no significant difference in CK-MB levels comparing ART-experienced to ART-naïve HIV positive subjects.[40]

In this study, subjects were not exposed to stavudine or didanosine which were common causes of mitochondrial damage and lactic acidosis. It is however worthy of note that troponin-1 level was raised in the users of tenofovir and nevirapin and that there was increased level of CK-MB in the users of tenofovir and efaverence although, these values were not statistically significant. Another study have shown significantly higher values of mitochondrial creatine kinase in patients on tenofovir.[41] It is advisable therefore that patients placed on these drugs especially tenofovir be monitored for increase in cardiac markers or by echocardiography.

CONCLUSION

The metabolic complications in HIV include dyslipidemia, hyperinsulinemia, hyperglycemia, insulin resistance, lactic acidosis, osteonecrosis and osteoporosis.[42,43] This study has shown that the presence of HIV with or without HAART reduces insulin sensitivity and modifies lipid metabolism. Therefore patients should be monitored for metabolic disorders before and after commencing HAART and nutritionists should be involved in management.

A limitation of the study is the small sample size which was deemed necessary because the study was funded by the authors. Participants had to be induced to present with overnight fasting for appropriate blood sampling.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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