ORIGINAL ARTICLE

# Correlation of selected inflammatory markers with cardiovascular diseases markers among HIV patients in Benin City, Nigeria

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## ABSTRACT

**Objectives:** Dyslipidaemia has been reported in HIV infections which often results in cardiovascular disease (CVD). Given that HIV is associated with inflammation with resultant adverse clinical outcomes, this study seeks to assess the correlation between selected markers of inflammation and markers of cardiovascular diseases among HIV patients in Benin City, Nigeria.
**Methods:** Selected inflammatory markers (such as Albumin, CD4, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII)) and markers of CVD (such as atherogenic index of plasma (AIP), Castelli's risk index(CRI), triglyceride-high density lipoprotein cholesterol ratio (TG/HDL-c) and triglyceride glucose index (TyG index)) were evaluated in 173 participants comprising 81 HIV patients on Highly Active Antiretroviral Therapy (HAART), 45 HAART-naïve HIV patients and 48 non-HIV individuals (Controls) attending out-patients clinics in the University of Benin Teaching Hospital, Benin City. Using blood samples obtained from each of the participants, albumin, CD4 count, Full blood count (FBC) and lipid profile test were determined using standard methods from where other markers were calculated.
**Results:** CD4 count and albumin were lower in HAART-naïve HIV patients than in both those on HAART and non-HIV ($P<0.001$) whereas PLR were higher. AIP and TG/HDL-c were significantly higher in HAART-naïve HIV patients than in those on-HAART and non-HIV subjects. In HAART-naïve patients, albumin with AIP, TyG index and TG/HDL-c, and CD4 with CRI and TG/HDL-c correlated negatively. This was the same for albumin with TyG index amongst HIV patients on HAART. In non-HIV patients, CRI had a significant positive correlation with NLR, PLR and SII, while CD4 with TG/HDL-c, AIP and TyG index was the reverse relationship. Using AIP and TG/HDL-c cut-off values, HAART naïve HIV patients had a higher risk of developing cardiovascular disease than non-HIV patients, followed by HIV patients on HAART.
**Conclusion:** This study showed that HIV is linked to lipid abnormalities as a result of chronic inflammation. Therefore, HIV patients should be monitored for inflammation and CVD.
**Keywords:** Albumin, Antiretroviral therapy, cardiovascular disease, HIV, inflammation

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## INTRODUCTION

Human immunodeficiency virus (HIV) patients on antiretroviral therapy (ART), particularly those on protease inhibitor-based regimens, have been found to have a variety of lipid abnormalities (1). Reports have shown that adults with HIV who have lipid abnormalities may be at risk for vascular permeability, arterial stiffness and cardiovascular disease (2-4). In HIV-positive people, the risk of cardiovascular abnormalities (especially coronary artery disease) is 1.5 – 2 times greater than in uninfected people. Although HIV infection and the antiretroviral therapy have been reported to be among the known conventional risk factors, persistent immunological activation and systemic inflammation that are crucial in HIV pathogenesis also increase the risk of coronary artery disease in HIV patients who are receiving ART as well as in those who have never received the drug (1,5).

Due to a variety of methodological issues, including differences in study designs, choices of inflammatory biomarker panels, and selection of clinically relevant outcomes, evaluating inflammatory biomarkers in the context of CVD risk in HIV-infected people is difficult especially in resource limited settings (6). However, some novel biomarkers such as atherogenic index of plasma (AIP), triglyceride-high density lipoprotein cholesterol (TG/HDL-c) ratio, triglyceride glucose index (TyG index) and Castelli's Risk Index (CRI) have been utilised as strong and reliable predictor of dyslipidaemia and related disorders such as cardiovascular diseases (7,8).

Recently, we had observed a correlation between some surrogate markers of inflammation and non-invasive markers of liver fibrosis (unpublished observation). Some of these earlier studied surrogate markers of inflammation such as platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR) have all been discovered as markers of inflammation in a variety of illnesses, including malignancies and cardiovascular disease (9-11).

Therefore, this study aims to assess the correlation of some surrogate inflammatory markers with some markers of cardiovascular disorders among HIV patients attending clinic in the University of Benin Teaching Hospital in Benin City, Nigeria.

## MATERIALS AND METHODS

### Study location and population

A total of 125 HIV patients were recruited for the study at the University of Benin Teaching Hospital in Benin City, Edo State, Nigeria. Of the 125 HIV patients, 81 (20 males and 61 females) were on Highly Active Antiretroviral Therapy (HAART), whereas the remaining 44 (18 males and 26 females) were HAART-naive. The study also included 48 (28 males and 20 females) HIV seronegative individuals who served as controls. All participants were asymptomatic. The ages of participants (mean ± standard deviation) across the groups were 40.64 ± 9.63years for HAART-naïve, 41.19± 11.57years for those on HAART and 30.36± 10.07years for controls. All participants were instructed to be on 10 – 12 hours fasting prior to specimen collection. Informed consent was obtained from all participants prior to specimen collection. The Ethical Committee of Edo State Ministry of Health, Benin City, Nigeria, approved the protocol for this study.

### Inclusion and exclusion criteria

Clinical stage I HIV patients and apparently healthy seronegative HIV subjects were recruited for this study. Subjects that were pregnant, diabetic, hypertensive, smokers, hepatitis B and C seropositive, as well as on lipid and glucose medications were excluded from this study.

### Sample collection and processing

Ten millilitres of blood was collected from each subject and dispensed in 5m/L amounts in ethylene diamine tetra acetic acid (EDTA), fluoride-oxalate and plain containers. The EDTA

blood was used for complete blood count and CD4 count, fluoride-oxalate specimen for glucose estimation and sera samples obtained were used to analyse some biochemical parameters (albumin, and lipid profiles) of all participants.

**Full Blood Count Analysis**

Complete blood count (CBC) was determined with the EDTA blood sample using haematology auto-analyser (Sysmex K2IN, Sysmex Corporation, Kobe, Japan) by following the manufacturer's instructions.

**CD4 Cell Count Estimation**

Flow cytometry was used for the CD4 cell count estimation using the Partec Cyflow Counter II® and the Sysmex CD4 Easy Count Kit® following the manufacturers' instruction.

**Biochemical Analysis**

Blood from fluoride-oxalate containers and sera samples were used to determine the following biochemical parameters – fasting blood glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), triglyceride (TG) and albumin using Selectra ProS chemistry auto analyser (Vital Scientific Inc., Germany) following the manufacturer's instruction. The low -density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald's equation as previously described (12).

**Inflammatory Markers**

Some inflammatory markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) were calculated from the obtained parameters of the CBC (11). Briefly, NLR was calculated as the ratio of the neutrophils count to lymphocyte counts and PLR was calculated as the ratio of the platelet count to lymphocyte counts. The SII was defined as: SII = neutrophil x platelet/lymphocyte.

**Markers of Cardiovascular Diseases**

The markers of cardiovascular diseases such as atherogenic index of plasma (AIP), Castelli's Risk Index (CRI), TG/HDL-c ratio and triglyceride glucose index (TyG index) were calculated from the obtained biochemical parameters as follows:

AIP was calculated as $\log_{10}$ (TG/HDL-c) and, according to previous studies, classified into three groups: low risk (<0.11), intermediate risk (0.11–0.21), and increased risk (>0.21) (13).

Castelli's Risk Index (CRI) is calculated as the ratio of TC to HDL-c. A value of ≥ 5 was associated with cardiovascular disease (14).

The TG/HDL-c ratio was calculated by dividing the serum concentration of TG by HDL-c measured in mg/dL and a cut-off for TG/HDL-c ≥ 3.5 has been reported to be associated with CVD (15). TyG index was calculated based on the formula: Ln (TG (mg/dL) x FG (mg/dL)/2) (16).

**Statistical Analysis**

The data obtained were analysed using the statistical software INSTAT® version 3.10 for Windows 7 (Graph Pad Inc., La Jolla, California, USA). The parametric data were analysed with ANOVA and correlation while the non-parametric data were analysed with chi-square ($\chi^2$) test. Statistical significance was set at $p<0.05$.

## RESULTS

In this study, comparing the levels of selected surrogate markers of inflammation with the various study groups shows that PLR was significantly higher in HAART-naive HIV patients than non-HIV patients and HIV patients on HAART at $p<0.001$. CD4 count and albumin levels of HAART naïve HIV patients were significantly lower than those of both HIV patients on HAART and non-HIV Patients ($p<0.001$). NLR and SII were also significantly higher in HAART-naïve patients compared with those on HAART ($p<0.05$) while NLR of HAART-naïve HIV patients was also significantly higher than that of non-HIV patients ($p<0.05$) (Table 1). The comparison of the markers of cardiovascular diseases among the study group reveals that AIP was significantly higher in HAART-naïve HIV patients than those on-HAART at $P<0.01$ and non-HIV patients at $P<0.001$. Although there was no statistically significant difference in the levels of TyG index and CRI amongst the study groups, TG/HDL-c ratio was significantly higher in HAART-naïve HIV patients than non-HIV patients ($p<0.05$) (Table 2).

The correlation of markers of cardiovascular disease with some surrogate markers of inflammation reveals that albumin significantly correlates negatively with AIP, TyG index and TG/HDL-c in HAART-naïve patients while CD4 also has the same relationship with CRI and TG/HDL-c in the same group whereas only albumin had a significant negative correlation with TyG index amongst HIV patients on HAART. CRI had a significant positive correlation with NLR, PLR and SII among non-HIV patients; also, CD4 count had a significant negative correlation with TG/HDL-c, AIP and TyG index in the same group of participants (Table 3).

Although, TyG index was not used in the determination of the risk of cardiovascular disease because there are no known cut-off values, the study however showed that there was no statistically significant difference in the use of CRI, AIP and TG/HDL-c in the determination of the risk of cardiovascular disease across the group ($p = 0.8973$) (Table 4). Using AIP, HIV patients on HAART had higher risk of developing cardiovascular disease than the other group as 52.27% of HAART-naïve HIV patients had high risk of cardiovascular disease compared to HIV patients on HAART (12.35%) and non - HIV patients (25.00%) ($p<0.001$) whereas non-HIV patients had lower risk of cardiovascular disease than the other groups ($p<0.0001$) and HIV patients on HAART had moderate risk of cardiovascular disease than the other groups ($p=0.0081$). (Table 4).

**Table 1.** Comparison of Some Surrogate Markers of Inflammation among the Study Groups.

| Parameters | HAART-naïve (n=44) | On HAART (n=81) | Non-HIV (n=48) | p values |
|---|---|---|---|---|
| Albumin | 4.09± 0.09$^{*,\dagger}$ | 4.59± 0.04$^{*}$ | 4.62± 0.04$^{\dagger}$ | 0.0001 |
| Neutrophil-to-Lymphocyte ratio (NLR) | 2.22 ± 0.74$^{a,b}$ | 1.07 ± 0.07$^{a}$ | 0.89 ± 0.11$^{b}$ | 0.0232 |
| Platelet-to-Lymphocyte ratio (PLR) | 203.72 ± 40.92$^{*,\dagger}$ | 103.33 ± 5.35$^{*}$ | 93.13 ± 7.63$^{\dagger}$ | 0.0002 |
| Systemic Immune-inflammatory Index (SII) | 699.70 ± 295.80$^{a}$ | 250.85 ± 23.35$^{a}$ | 210.35 ± 28.56 | 0.0313 |
| CD4 count (cells/μL) | 261.27 ± 29.02$^{*,\dagger}$ | 520.16 ± 29.40$^{*}$ | 613.07 ± 38.53$^{\dagger}$ | 0.0001 |

Values are mean ± SEM; *,† = $p<0.001$; a,b = $P<0.05$

**Table 2**. Comparison of markers of cardiovascular disease among the study groups.

| Parameters | HAART-naïve (n=44) | On HAART (n=81) | Non-HIV (n=48) | P values |
|---|---|---|---|---|
| Atherogenic Index of Plasma (AIP) | 0.23 ± 0.04*, † | 0.09 ± 0.02* | 0.05 ± 0.04† | 0.0006 |
| Triglyceride-HDL-c Ratio (TG/HDL-c) | 1.98 ± 0.19# | 1.44 ± 0.16 | 1.28 ± 0.11# | 0.0185 |
| TyG Index | 8.42 ± 0.09 | 8.31 ± 0.07 | 8.17 ± 0.08 | 0.1375 |
| Castelli's Risk Index (CRI) | 2.96 ± 0.12 | 2.85 ± 0.08 | 3.05 ± 0.25 | 0.6041 |

Values are mean ± SEM; * = p<0.01, † = p<0.001; # = p<0.05

**Table 3:** Correlation of Markers of Cardiovascular Disease with some surrogate markers of inflammation

| Inflammatory markers | CRI | TG/HDL-c | AIP | TyG Index |
|---|---|---|---|---|
| HAART-naïve | | | | |
| Albumin | -0.1855 | -0.5864* | -0.5866* | -0.4750* |
| CD4 | -0.3446* | -0.3217* | -0.2748 | -0.0671 |
| NLR | 0.1126 | 0.2727 | 0.2707 | 0.2255 |
| PLR | 0.0831 | 0.2053 | 0.2254 | 0.2244 |
| SII | 0.0862 | 0.2429 | 0.2477 | 0.2181 |
| On HAART | | | | |
| Albumin | 0.0953 | 0.0271 | 0.0137 | 0.3132* |
| CD4 | -0.0739 | 0.0144 | -0.0995 | -0.1664 |
| NLR | -0.0187 | -0.0695 | 0.0321 | 0.0736 |
| PLR | -0.0348 | -0.0535 | -0.0102 | 0.0043 |
| SII | -0.0551 | -0.0719 | 0.0244 | 0.1068 |
| Non-HIV | | | | |
| Albumin | -0.0526 | 0.0411 | 0.0647 | -0.0251 |
| CD4 | -0.2208 | -0.3259* | -0.4007* | -0.3793* |
| NLR | 0.6562* | 0.2501 | 0.1812 | 0.1772 |
| PLR | 0.3385* | 0.0594 | 0.0409 | 0.0974 |
| SII | 0.6685* | 0.2050 | 0.1357 | 0.1065 |

*Significant correlation (p<0.05)

**Table 4.** Prevalence of Risk of Cardiovascular Disease among study population

| | HAART-naïve (n=44) | On HAART (n=81) | Non-HIV (n=48) | P value |
|---|---|---|---|---|
| **CRI** | 0 ( 0.00) | 2(2.47) | 1( 2.08) | 0.5864 |
| **TG/HDL-c** | 4 (9.09) | 3 (3.70) | 2 (4.17) | 0.4020 |
| **AIP** | | | | |
| Low Risk <0.11 | 4 (9.09) | 41 (50.62) | 27 (56.25) | <0.0001 |
| Moderate Risk 0.11- 0.21 | 7 (15.91) | 30 (37.04) | 8 (16.67) | 0.0081 |
| High Risk >0.21 | 23 (52.27) | 10 (12.35) | 12 (25.00) | <0.0001 |

Values are number (Percentage %)

## DISCUSSION

Infection with the human immunodeficiency virus (HIV) and subsequent antiretroviral therapy (ART) are frequently associated with lipid profile changes. Furthermore, despite the fact that antiretroviral therapy (ART) suppresses viral replication, prolonged inflammation is expected to cause changes in lipid composition and function, increasing the risk of cardiovascular disease (CVD) (17). Therefore, this study which seeks to examine the correlation of some surrogate markers of inflammation with some markers of cardiovascular disease has some interesting findings.

Hypoalbuminemia has been established as the result of the combined effects of inflammation and inadequate protein and caloric intake in patients with chronic diseases such as chronic renal failure (18). This agrees with the findings in our study, where albumin levels in HAART naïve HIV patients were significantly lower than its level in HIV patients on HAART and non-HIV patients because HAART naïve HIV patients have more inflammation than the other groups. PLR have been shown to be markers of systemic inflammation and predict mortality in the general population, whether or not they are infected with HIV (19). As a result of viral suppression following HAART commencement, there was substantially higher PLR values in HAART naive HIV patients than in HIV patients on HAART. As a result, the significantly higher PLR levels and lower CD4 counts in HAART naive HIV patients compared to the other groups in our study reflects the severity of the underlying systemic inflammatory and coagulation disturbances that lead to increased mortality in HIV positive people without HAART (20).

Our study also compared the markers of cardiovascular disease among the various study groups; the findings of AIP and TG/HDL-c being significantly higher in HAART-naïve compared to non-HIV patients is consistent with several previous studies (21-24). However, contrary to some of these studies that have identified higher prevalence of dyslipidaemia in HIV patients undergoing treatment with HAART, our study has shown that the level of some markers of cardiovascular disease were higher in HAART naïve HIV patients compared to those on HAART. This may be due to the fact that most of these studies used the levels of lipid profile parameters for assessment, unlike our study where we used novel biomarkers of cardiovascular disorders and may also be due to the fact that all HIV patients in our study were not known to have progressed beyond clinical stage one. Furthermore, studies have revealed that AIP may serve as a diagnostic alternative in situations where other atherogenic risk parameters such as TG appear normal and that it has a role in predicting CVD risk and treatment success. In the same vein, high ratio of TG/HDL-c has been strongly indicated to correlate with coronary disease than lipid variables (25-27). Our finding further buttresses the fact that HIV as an inflammatory disease induces dyslipidaemia in a lot of people living with it to the extent that cardiovascular disease (CVD) is currently the second most frequent cause of death (after cancer) among HIV-positive subjects (28,29).

However, the observed non statistically significant difference in the levels of TyG index and CRI among the different study group in our study agrees with the report of Kamoru and colleagues being a study done in a similar setting as ours (23). This therefore implies that these markers may not be good markers for assessment of cardiovascular diseases in our locality. However, the claim that before initiation of antiretroviral medication, an HIV-positive person's lipid metabolism is severely disrupted and that ART resets the balance, sometimes for the better, sometimes for the worse justifies our findings in this research (30).

Our study also revealed that a significant relationship exists between some markers of cardiovascular disease with some surrogate markers of inflammation in HAART-naïve HIV patients especially albumin and CD4 counts. Although there is paucity of data on the relationship between the surrogate markers of inflammation used in this study and markers of cardiovascular disease, some studies have identified that there is a relationship with inflammatory markers and cardiovascular diseases as inflammation arising from HIV infection modulates lipid particle and lipid transport (18). The mechanism by which this happens is that inflammation impairs reverse cholesterol transfer (RCT), in which HDL-c transports atherogenic lipid molecules from atherosclerotic plaques for elimination by the liver (30). Also, a variety of ATP-binding cassette transporters (ABC transporters) in the arterial wall like macrophages ferry atherogenic lipid molecules onto HDL-c or ApoA1 for reverse cholesterol efflux, commencing RCT and leading to cholesterol excretion (30). Therefore, our findings in this study suggests that these surrogate inflammatory markers can also be assessed as a predictor of developing cardiovascular disorders in HIV patients.

Finally, we also observed that the HAART-naïve HIV patients had higher risk of developing cardiovascular disease among the study groups in our study. This finding is consistent with other studies that have associated HAART-naïve HIV patients with higher risk of cardiovascular diseases (3-5,7). This finding establishes that the link between HIV infection and dyslipidaemia is inflammation as HAART-naïve HIV patients had more inflammation on higher risk of cardiovascular disease.

This study has some limitations like not including demographic and anthropometric data in the analysis as well as not inquiring about the risk factors for cardiovascular diseases among study participants, it is however, believed that this can become a follow-up study.

In conclusion, our study has observed that HIV is associated with lipid disturbances which is a result of persistent inflammation, hence the need to monitor inflammation and CVD markers in HIV.


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### Conflict of Interest

The authors report no conflict of interest in the course of this research.

## AUTHOR CONTRIBUTIONS

GAA and RO conceptualised the study. GAA, NLI, ROA and RO carried out sample collection and analysis. NLI and RO analysed data and drafted the manuscript. GAA, ROA and RO contributed to reviewing and finalising the manuscript. All Authors approved the final version of the manuscript.

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