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Evaluation of Cardiovascular Risk Factors and Metabolic Abnormalities in HIV Subjects on Therapy

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Abstract

The study recruited 154 HIV seropositive subjects visiting HIV Clinic at Abia State University Teaching Hospital, Aba. They were stratified into four groups. Group 1 and 2 were made up of 25 males and 62 females HIV seropositive subjects who were not yet on antiretroviral therapy, while group 3 and 4 are made up of 26 males and 41 females who were already on routine antiretroviral therapy (a combination of Lamivudine 150 mg, Zidovudine 300 mg and Nevirapine 200 mg) at least for the past 12 months. The age range of the study subjects was 15 to 55 years. Also, a total of 50 HIV seronegative subjects, made up of 20 males and 30 females participated in the study. They served as controls. The age range was 18 to 50 years. The study evaluated the cardiovascular risk factors and metabolic abnormalities in HIV seropositive subjects on therapy was categorized into biomarkers namely: Cardiovascular, metabolic, immunologic, renal function and haematologic markers. The cardiovascular markers evaluated include; serum lipids and high sensitivity c-reactive protein. HIV seropositive subjects who were not on therapy (non-ART) had decreased serum levels of total cholesterol ($P < 0.001$), no significant decreased serum levels of low-density lipoprotein and high-density lipoprotein cholesterols, as well as elevated mean ± SEM serum levels of triglyceride ($P < 0.001$) and high sensitivity C-reactive protein ($P < 0.001$) compared with HIV naïve subjects were observed. On the other hand, HIV seropositive subjects on antiretroviral therapy (ART) showed hypercholesterolemia, hypertriglyceridemia and elevated high sensitivity C-reactive protein ($P < 0.001$). LDL-cholesterol was not significantly increased and HDL-cholesterol was not significantly decreased. Upon comparison of cardiovascular markers in non-ART and ART subjects in both genders, in male ART subjects, results showed increased serum levels of total cholesterol (251.160 ± 9.106 mg/dl vs 238.76 ± 7.538 mg/dl), LDL-C (96.60 ± 5.584 mg/dl vs 88.20 ± 5.652 mg/dl), HDL-C (62.75 ± 2.725 mg/dl vs 56.52 ± 2.546 mg/dl), triglyceride (420.36 ± 30.184 mg/dl vs 398.64 ± 23.693 mg/dl) and high sensitivity c-reactive protein (3.616 ± 0.516 mg/dl vs 1.92 ± 0.601 mg/dl). The female subjects recorded similar result pattern with the male. The metabolic markers evaluated serum glucose, insulin, electrolytes and aminotransferases. In both genders, hyperinsulinemia was revealed in ART subjects with normoglycemia in both ART and non-ART subjects. Mean ± SEM serum electrolyte levels were not significantly reduced in non-ART subjects compared with ART subjects. However, they were all within the normal reference range. In male non-ART subjects, mean ± SEM serum levels of ALT (53.64 ± 3.768 iu/L) and AST (60.16 ± 3.432 iu/L) were not significantly increased when compared with ART subjects, ALT (42.52 ± 5.596 iu/L) and AST (46.24 ± 5.100 iu/L). In female subjects, the variation of the serum enzyme

levels were very minor. The immunologic markers evaluated were CD4 cell count, CD3 cell count and high sensitivity C-reactive protein. CD4 cell count was significantly decreased in non-ART subjects compared with HIV naïve subjects ($P < 0.001$) while high sensitivity C-reactive protein serum mean ± SEM was significantly elevated in ART subjects ($P < 0.001$) and non-ART subjects ($P < 0.05$) respectively compared with HIV seronegative subjects. The degree of CD4 cell counts reduction was more in the non-ART subjects compared with the ART subjects in both male and female subjects. On the other hand, the degree of hsCRP elevation was more on ART subjects compared with non-ART subjects in both genders ($P < 0.001$). The renal function markers evaluated weight, serum creatinine and creatinine clearance levels. There was reduction in the weight of non-ART subjects (58.724 ± 1.341 kg) and ART subjects (62.075 ± 1.358 kg) respectively compared with HIV seronegative subjects (67.72 ± 1.503 kg). Also, the mean ± SEM serum clearance levels were elevated in non-ART subjects (0.783 ± 0.0953 mg/dl) and ART subjects (0.732 ± 0.0315 mg/dl). Also, the creatinine clearance was reduced in non-ART subjects (128.722 ± 4.110 ml/min) and ART subjects (131.376 ± 4.511 ml/min) respectively compared with HIV naïve subjects (149.47 ± 2.979 ml/min). In male subjects, creatinine clearance was reduced in ART subjects compared with non-ART subjects. Serum creatinine level was also not significantly higher in ART subjects compared with non-ART subjects. This discordant was due to weight disparity. Non-ART subjects had higher weight than ART subjects. On the other hand, the reverse was recorded in female subjects. Non-ART subjects had non-significantly lower creatinine clearance value, and higher serum clearance level and reduced mean ± sem weight when compared with ART subjects. The haematological markers revealed remarkable abnormalities in both male and female subjects, where statistically significant thrombocytopenia, anaemia, neutropenia and lymphocytosis were recorded in non-ART subjects compared with ART subjects and HIV naïve subjects respectively ($P < 0.001$). In both genders, moderate increases in monocyte and decreases in total white blood cell count were recorded in non-ART subjects.

Keywords: *HIV; AIDS; Antiretroviral; Cardiovascular; HAART*

Introduction

Acquired Immunodeficiency Syndrome (AIDS) was first reported in the United States of America. In June 1981, the Center for Disease control and prevention (CDC) reported that five young homosexual men in the Los Angeles area had contracted *Pneumocystis cavini* pneumonia. Two of the subjects had died [1]. This report signaled the beginning of a pandemic of a retroviral disease characterized by profound immunosuppression, that leads to opportunistic infections, secondary neoplasms and neurologic manifestations.

This disease has come to be known as acquired immunodeficiency syndrome. This fatal disease is caused by the retrovirus, human immunodeficiency virus (HIV). When it was first isolated in 1983, it was referred to as Lymphadenopathy associated virus (LAV) and Human T-lymphotropic virus (HTLV). In 1986, the name, Human Immunodeficiency Virus (HIV) was officially given to the virus by the International Committee on the Taxonomy of virus [2].

The Acquired Immunodeficiency syndrome (AIDS) is a global health problem and is the major cause of death in men and women between the ages of 20 and 50 years worldwide [3]. The major metabolic abnormalities that occur during the course of HIV infection include dyslipidaemia, morphological changes and dysregulation of glucose metabolism [4].

The natural history of HIV infection changed abruptly in 1995 subsequent to the introduction of highly active antiretroviral therapy (HAART), resulting in markedly lower mortality rates [5]. Treatment of HIV/AIDS with potent antiretroviral therapy has transformed human immunodeficiency virus infection from a rapidly fatal disease into a chronic illness that some subjects can live with for more than two decades. With the introduction of antiretroviral therapy, one would assume that metabolic changes associated with HIV/AIDS would reverse themselves as immune stimulants and inflammatory agents decreased along with HIV viral load. Instead, the lipid abnormalities intensified [6].

There has been much concern on the emergence of this metabolic and amorphological changes, collectively referred to as lipodystophy as a significant issue in subjects being treated for HIV infection and its consequences for the long-term management of HIV/AIDS. It is believed, the metabolic manifestation of lipodystrophy may contribute to a range of morbidities most notably cardiovascular disorders [7].

Some scientists attributed the raised lipid levels to the increase of interferon-alpha (IFN-alpha) and C-reactive protein productions occurring during HIV infection. These acute phase proteins, especially IFN-alpha, is an antiviral signaling molecule that renders cells less hospitable to viral infection [8]. Others suggested that underlying this complex clinical picture is an equally complex series of interconnected molecular disturbances. Arising secondary to the effects of HIV infection itself, direct drug-induced toxicities and indirect effects of changes in body composition on other aspect of lipid metabolism [9]. The long-term risk of atherosclerotic cardiovascular disease for subjects who experience increase in atherogenic serum lipids, insulin resistance/dysglycaemia and body fat redistribution is a great concern. To access the aetiology of these metabolic abnormalities and its relevance to current approaches to HIV management, it is believed that evaluation of changes in serum lipid levels abnormalities in HIV subjects and on therapy perhaps, will lead to understanding of the potential consequences of such changes for risk of adverse cardiovascular events and related metabolic abnormalities.

In line with the above objective, this study will be on: Evaluation of Cardiovascular risk factors and metabolic abnormalities in HIV subjects and on therapy. The scope will cover estimation of serum levels of conventional lipids of cardiovascular risk importance, high sensitivity c-reactive protein, insulin, glucose, electrolytes, transaminases, CD4, CD3 creatine and creatinine clearance. The major metabolic abnormalities that occur during the course of HIV/AIDS infection and therapy include dyslipidaemia, morphologic changes and dysregulation of glucose metabolism. The long-term risk of atherosclerotic cardiovascular disease for subjects with increased atherogenic serum lipids is of clinical concern [10]. Some scientists are of the view that emergence of metabolic abnormalities such as dyslipidaemia, insulin resistance, diabetes mellitus and lactic acidaemia are significant issues in subjects undergoing antiretroviral therapy (ART) [11]. The consequence for the long-term management of HIV/AIDS is the risk of atherosclerotic, cardiovascular disease. This is therapeutically and clinically challenging as management of HIV/AIDS subjects lifetime antiretroviral therapy. The specific risk attributed to HIV infection and to therapy related metabolic changes remains incompletely defined. The aetiology of these lipid abnormalities remains uncertain. Many opinions agree that it is likely to be multifactorial: the individual contributions of HIV infection, specific antiretroviral agents, host genetics and body fat changes. All are likely to contribute to the metabolic abnormalities [11].

On the other hand, it is believed that abnormalities in blood lipid begin early in HIV infections. This is attributed to changes to the increase of interferon alpha (IFN-alpha) production occurring during HIV infection [12]. There is no doubt that effective antiretroviral therapy has resulted in a dramatic decline in HIV related mortality. However, many HIV infected subjects are likely to experience some health challenges including the risk of cardiovascular disease and metabolic abnormalities. The critical question therefore, is, to what extent HIV and/or its treatment accelerates the risk that subjects already faced?

In an attempt to find an answer to the question, research on Evaluation of Cardiovascular risk and metabolic abnormalities in HIV subjects and therapy is necessary. Perhaps, it will offer a better understanding of the mechanisms underlying the metabolic activities disturbances as well as provide vital scientific information for the development of patient friendly antiretroviral drugs.

Also, previously, it was thought that cardiovascular disease was simply the result of lipid deposit in the cardiac arteries. However, the disease is now viewed as a process that involves multiple elements with chronic inflammation playing a significant role. It is believed that c-reactive protein, especially high sensitive C-reactive protein, a biomarker of microorganism inflammation, may predict future cardiovascular risk [13].

To reach a specific diagnostic conclusion that is supported by current scientific knowledge, the use of specific biomarker becomes an imperative. Also, to triage the concomitant adverse events of antiretroviral therapy that will improve the management of HIV subjects in the battle against the virus.

Aim of the Study

The aim of the study is to evaluate the potentials of HIV/AIDS and currently available antiretroviral agents. Their roles in increasing serum concentrations of biochemical cardiovascular risk markers and some abnormalities of metabolic indicators.

Materials and Methods

Study site

Subjects were seen at HIV/AIDS clinics of Abia State University Teaching Hospital (ABSUTH) Aba. The analyses of the samples were done at their different laboratories in the city based on the availability of facilities. They are HIV/AIDS laboratories, Abia State University Hospital Aba, New Covenant laboratories and Gamma Medical Laboratories, Aba. Aba is the largest and commercial city in Abia State. The city constituted a favorable site for the study. It is the most populated city in the state and has the highest number of people living with HIV/AIDS. The Abia State University Teaching Hospital in which the samples were collected comes first in the care of people living with HIV/AIDS in Abia State. The hospital receives subjects from other ports of the state due to its consistent supply of materials by international donor agents for the treatment and management of HIV/AIDS subjects.

Study design

There were 204 subjects selected in this study aged between 15 and 55 years. They were grouped into 6 groups. 25 male HIV-seropositive subjects on antiretroviral therapy, 62 female HIV-seropositive on antiretroviral therapy. 26 male HIV-seropositive non-ART and 41 female HIV-seropositive non-ART subjects. And 20 male HIV-seronegative and 30 female HIV-seronegative control subjects. At the initial stage of the study, appropriate advocacy was carried out and all participants provided informed consent and assurance of confidentiality of identity granted.

Subjects

A total of 104 HIV-seropositive subjects were enlisted, made up 0f 26 males and 41 females who were diagnosed with HIV infection and have been on treatment at least 12 months, and currently receiving antiretroviral therapy that contains at least 2 nucleotide reverse transcriptase inhibitors (NRTIS) and 1 non-nucleotide reverse transcriptase inhibitor (NNRT). And 62 females and 25 male subjects who were diagnosed HIV positive, but have not commenced antiretroviral treatment.

Control subjects: A total of 50 volunteer control subjects participated in the study made up of 20 males and 30 females, ages between 20 to 50 years. They served as control for comparative analysis of the findings of the study. They were HIV-seronegative males and females living in Aba metropolis in the past one year.

Selection criteria

Inclusion criteria (Subjects): Subjects confirmed to have HIV by western blot and seen at HIV/AIDS clinics within the study period:

- Subjects that were within the age bracket of 15 - 55 years.
- HIV drug naïve subjects and subjects who had been on antiretroviral drugs for not less than 12 months.

Inclusion criteria (Control)

- HIV sero-negative subjects.
- Age and gender matched subjects.

Exclusion criteria

- Diabetes mellitus subjects.
- Subjects with hypertension.
- Subjects with cardiovascular disease.
- Subjects with renal disease.

Blood collection

Blood samples were collected from the vein. 5 mls of blood was collected using sterile disposable non-progenic syringe into dry vacutainer and 0.5 mls dispensed into clean EDTA container for CD4 and CD3 count. The samples were appropriately labeled to reflect codes given to subjects. After clotting the samples were separated to collect the serum using centrifuge for the future batch analysis.

Reagents for biochemical analysis

All the reagents used for estimation of serum levels of lipid profile, creatinine, glucose and aminotransferases were commercial kits prepared by Randox Laboratories Ltd < 55 diamond Road, Crumlin co. Antrim, United Kingdom.

Reagents for high sensitivity C-reactive protein [hsCRP]: Commercial kit was used for the serum quantitative determination of high sensitivity C-reactive protein. The kit was prepared by immunospec corporation. 7018 Owensmouth Ave, suite 103 canoga park, CA, 91303. U.S.A.

Reagents for human insulin: Commercial kit was used for quantitative determination of insulin in serum. Prepared by immunospec Corporation, U.S.A.

Reagents for CD4 count: Partec Tube, PE-conjugated monoclonal antibody, Buffer, Control bead and Fixative solution.

Statistical analysis

Data were entered into Microsoft excel, 2010 (Microsoft Corporation Inc, USA) and transported to the software package SPSS for windows version 20.0 for analysis. The study participants were grouped as: HIV negative individuals, HIV positive subjects on ART and ART naïve HIV positive subjects. Differences between group means were compared using the student's t-test or analysis of variance (ANOVA). Spearman's rho correlation was used to assess the relationship between non-parametric data. Statistical significance was set at $P \leq 0.05$.

Results

The potential for cardiovascular risk and metabolic abnormalities in HIV and therapy were evaluated in 154 HIV seropositive subjects. They were made up of 26 males and 41 females who have commenced antiretroviral therapy and 25 males and 62 females who were not on therapy. Also 50 HIV seronegative subjects participated in the study as control made up of 20 males and 30 females respectively. The results were compared into cardiovascular, metabolic, immunologic, renal function and haematologic markers. The summary of the results is presented below.

Evaluation of cardiovascular parameters in the groups of the study population

Parameter	Control Subjects Mean ± SEM n = 50	ART subjects Mean ± SEM n = 67	Non-ART subjects Mean ± SEM n = 87
TC (mg/dl)	259.345 ± 8.536	260.5 ± 5.795 (0.000)*	208.34 ± 4.193(0.000)*
LDL-C (mg/dl)	106.126 ± 6.269	107.00 ± 4.132 (0.640)	104.56 ± 2.363 (0.854)
HDL-C (mg/dl)	67.03 ± 1.907	60.657 ± 1.957 (0.629)	62.793 ± 1.802 (0.108)
TC/HDL-C	3.750 ± 0.671	4.298 ± 0.732 (0.432)	3.317 ± 0.671 (0.778)
TG (mg/dl)	131.92 ± 8.195	435.86 ± 18.565(0.00)*	391.82 ± 12.356(0.00)*
hsCRP (mg/dl)	1.404 ± 0.148	4.822 ± 0.429 (0.000)*	2.649 ± 0.208 (0.005)
df		115	131

Table 1: *Comparison of cardiovascular risk parameters in male and female HIV seropositive subjects who were on/ not on antiretroviral therapy with control subjects.*

*Key: TC = Total Cholesterol; TG = Triglyceride; LDL-C = Low Density Lipoprotein Cholesterol; ART= Antiretroviral Therapy; hsCRP = High Sensitivity C-Reactive Protein; HDL-C = High Density Lipoprotein; TC/HDL-C = Total Cholesterol/High Density Lipoprotein Cholesterol; *P < 0.001; ** P < 0.005.*

Parameter	Male Control Subjects Mean ± SEM n = 20	Male ART subjects Mean ± SEM n = 26	Male Non-ART subjects Mean ± SEM n = 25
TC (mg/dl)	238.96 ± 7.535	251.16 ± 9.106 (0.003)	216.25 ± 6.264 (0.044)
LDL-C (mg/dl)	92.64 ± 5.584	103.15 ± 2.161 (0.341)	88.20 ± 5.652 (0.006)
HDL-C (mg/dl)	67.960 ± 3.226	62.75 ± 2.725 (0.243)	56.52 ± 2.546 (0.043)
TC/HDL-C (mg/ dl)	3.446 ± 0.310	3.696 ± 0.521 (0.256)*	4.224 ± 0.712 (0.431)
TG (mg/dl)	164.25 ± 11.193	420.36 ± 30.184 (0.00)*	398.64 ± 23.693 (0.00)*
hsCRP (mg/dl)	1.645 ± 0.248	3.616 ± 0.516 (0.002)	1.92 ± 0.601 (0.005)
Df		44	43
Parameter	**Female Control Subjects Mean ± SEM n = 30**	**Female ART subjects Mean ± SEM n = 41**	**Female Non-ART subjects Mean ± SEM n = 62**
TC (mg/dl)	227.822 ± 11.47	265.31 ± 7.537 (0.000)*	203.066 ± 5.475 (0.002)*
LDL-C (mg/dl)	105.50 ± 3.556	112.97 ± 5.652 (0.279)	83.355 ± 8.487 (0.531)
HDL-C (mg/dl)	70.333 ± 2.491	68.90 ± 2.546 (0.757)	63.322 ± 2.382 (-1.304)
TC/HDL-C	2.88 ± 0.071	3.851 ± 0.961 (0.572)	3.947 ± 0.613 (0.752)
TG (mg/dl)	110.366 ± 9.715	439.85 ± 23.692 (0.00)**	389.064 ± 14.83 (0.00)**
hsCRP (mg/dl)	1.243 ± 0.181	5.573 ± 0.601 (0.000)***	3.185 ± 0.423 (0.002)***
Df		69	90

Table 2: *Comparison of cardiovascular risk parameters in HIV seropositive subjects on/not on antiretroviral therapy with control subjects.*

Parameter	Male ART subjects Mean ± SEM n = 26	Male Non-ART subjects Mean ± SEM n = 25
TC (mg/dl)	251.16 ± 9.106	216.25 ± 6.264 (0.297)
LDL-C (mg/dl)	103.15 ± 2.161	88.20 ± 5.652 (0.210)
HDL-C (mg/dl)	62.75 ± 2.725	56.52 ± 2.546 (0.002)
TC/HDL-C	3.696 ± 0.521	4.224 ± 0.712 (0.627)
TG (mg/dl)	420.36 ± 30.184	398.64 ± 23.693 (0.527)
hsCRP (mg/dl)	3.616 ± 0.516*	1.92 ± 0.601 (0.000)*
df	49	
Parameter	**Female ART subjects Mean ± SEM n = 41**	**Female Non-ART subjects Mean ± SEM n = 62**
TC(mg/dl)	265.31 ± 7.537	203.066 ± 5.475(0.573)
LDL-C (mg/dl)	112.97 ± 5.652	83.355 ± 8.487 (0.994)
HDL-C (mg/dl)	68.90 ± 2.546	63.322 ± 2.382 (0.283)
TC/HDL-C	3.851 ± 0.961	3.947 ± 0.613 (0.873)
TG (mg/dl)	439.85 ± 23.692*	389.064 ± 14.83 (0.042)*
hsCRP (mg/dl)	5.573 ± 0.601**	3.185 ± 0.423 (0.001)**
df	101	

Table 3: *Comparison of cardiovascular risk parameters in HIV subjects on antiretroviral therapy with HIV subjects who were not on therapy.*

Evaluation of metabolic parameters in the study population

Parameter	Control Subjects Mean ± SEM n = 50	ART subjects Mean ± SEM n = 67	NON-ART subjects Mean ± SEM n = 87
GLU (mg/dl)	72.80 ± 11.47	89.448 ± 3.214 (0.000)*	91.149 ± 3.0201 (0.000)*
INS (iu/L)	4.982 ± 0.379	12.845 ± 1.422 (0.000)*	7.301 ± 0.846 (0.047)
Na^+ (mmol/L)	137.76 ± 0.489	137.985 ± 0.452 (0.071)	135.839 ± 0.46 (0.198)
K^+ (mmol/L)	4.018 ± 0.0491	4.088 ± 0.065 (0.424)	3.993 ± 0.0603 (0.77)
Cl^- (mmol/L)	103.28 ± 0.653	105.089 ± 0.646 (0.056)	102.782 ± 0.607 (0.598)
CO_3^- (mmol/L)	24.84 ± 0.339	25.896 ± 0.397 (0.055)	24.195 ± 0.378 (0.253)
ALT (iu/L)	30.52 ± 1.797	39.00 ± 3.110 (0.00)	41.528 ± 3.742 (0.034)
AST (iu/L)	29.96 ± 1.474	39.88 ± 2.887 (0.007)*	45.689 ± 4.61 (0.002)*
df		115	131

Table 4: *Comparison of metabolic parameters in male and female HIV infected subjects on/not on therapy.*

*Key: GLU = Glucose; K^+ = Potassium; ALT = Alanine Aminotransferase; INS = Insulin; Cl^- = Chloride; AST = Aspartate Aminotransferase; Na^+ = Sodium; CO_3^- = Bicarbonate; * P < 0.001; ** P < 0.005.*

Parameter	Male Control Subjects Mean ± SEM n = 20	Male ART Subjects Mean ± SEM n = 26	Male NON-ART Subjects Mean ± SEM n = 25
GLU (mg/dl)	75.85 ± 2.180	92.52 ± 7.463 (0.069)	91.12 ± 2.683 (0.001)
INS (iu/L)	5.19 ± 0.675	8.496 ± 1.432 (0.059)	2.76 ± 2.040 (0.002)
Na^+ (mmol/L)	137.15 ± 0.938	137.902 ± 0.491 (0.442)	136.24 ± 0.491 (0.474)
K^+ (mmol/L)	4.040 ± 0.66	4.029 ± 0.0691 (0.246)	4.15 ± 0.091 (0.491)
Cl^- (mmol/L)	102.60 ± 1.219	103.72 ± 1.306 (0.574)	102.48 ± 0.672 (0.940)
CO_3^- (mmol/L)	25.65 ± 0.378	26.80 ± 0.529 (0.082)	24.88 ± 0.547 (0.452)
ALT (iu/L)	32.30 ± 2.213	42.52 ± 5.596 (0.167)	53.64 ± 3.768 (0.099)
AST (iu/L)	33.05 ± 1.975	46.24 ± 5.100 (0.037)	60.16 ± 3.432 (0.085)
df		44	43
Parameter	**Female Control Subjects Mean ± SEM n = 30**	**Female ART subjects Mean ± SEM n = 41**	**Female NON-ART subjects Mean ± SEM n = 62**
GLU (mg/dl)	70.76 ± 1.568	87.805 ± 2.682 (0.000)*	89.145 ± 3.738 (0.001)*
INS (iu/L)	4.843 ± 0.452	15.717 ± 2.040 (0.000)*	9.12 ± 1.098 (0.009)*
Na^+ (mmol/L)	136.50 ± 0.531	137.809 ± 0.488 (0.065)	135.677 ± 0.553 (0.351)
K^+ (mmol/L)	4.003 ± 0.069	4.026 ± 0.088 (0.817)	3.931 ± 0.066 (0.498)
Cl^- (mmol/L)	103.733 ± 0.730	105.976 ± 0.672 (0.025)	102.903 ± 0.752(0.489)
CO_3^- (mmol/L)	24.300 ± 0.485	25.414 ± 0.547 (0.197)	23.919 ± 0.404 (0.572)
ALT (iu/L)	29.333 ± 2.614	37.244 ± 3.768 (0.105)	36.645 ± 2.567 (0.079)
AST (iu/L)	27.900 ± 2.011	36.537 ± 3.437 (0.065)	39.855 ± 3.269 (0.012)
df		69	90

Table 5: *Comparison of metabolic parameters in HIV subjects on/not on therapy.*

Parameter	Male ART subjects Mean ± SEM (n = 26)	Male NON-ART subjects Mean ± SEM (n = 25)	Significant Level
GLU (mg/dl)	92.52 ± 7.463 (0.069)	91.12 ± 2.683 (0.001)	0.614
INS (iu/L)	8.496 ± 1.432 (0.059)	2.76 ± 2.040 (0.002)	0.000
Na^+ (mmol/L)	137.902 ± 0.491 (0.442)	136.24 ± 0.491 (0.474)	0.122
K^+ (mmol/L)	4.029 ± 0.0691 (0.246)	4.15 ± 0.091 (0.491)	0.852
Cl^- (mmol/L)	103.72 ± 1.306 (0.574)	102.48 ± 0.672 (0.940)	0.488
CO_3^- (mmol/L)	26.80 ± 0.529 (0.082)	24.88 ± 0.547 (0.452)	0.520
ALT (iu/L)	42.52 ± 5.596 (0.167)	53.64 ± 3.768 (0.099)	0.328
AST (iu/L)	46.24 ± 5.100 (0.037)	60.16 ± 3.432 (0.085)	0.317
Df	44	43	

Parameter	Female ART subjects Mean ± SEM (n = 41)	Female NON-ART subjects Mean ± SEM (n = 62)	Significant Level
GLU (mg/dl)	87.805 ± 2.682 (0.000)*	89.145 ± 3.738 (0.001)*	0.830
INS (iu/L)	15.717 ± 2.040 (0.000)*	9.12 ± 1.098 (0.009)*	0.003
Na^+ (mmol/L)	137.809 ± 0.488 (0.065)	135.677 ± 0.553 (0.351)	0.006
K^+ (mmol/L)	4.026 ± 0.088 (0.817)	3.931 ± 0.066 (0.498)	0.360
Cl^- (mmol/L)	105.976 ± 0.672 (0.025)	102.903 ± 0.752 (0.489)	0.004
CO_3^- (mmol/L)	25.414 ± 0.547 (0.197)	23.919 ± 0.404 (0.572)	0.042
ALT (iu/L)	37.244 ± 3.768 (0.105)	36.645 ± 2.567 (0.079)	0.861
AST (iu/L)	36.537 ± 3.437 (0.065)	39.855 ± 3.269 (0.012)	0.455
Df	101		

Table 6: *Comparison of metabolic parameters in male and female HIV subjects on therapy with male and female HIV subjects on/not on therapy.*

Evaluation of immunologic parameters in the study population

Parameter	Control Subjects Mean ± SEM (n = 50)	ART subjects Mean ± SEM n = 67	Non-ART subjects Mean ± SEM (n = 87)
$CD4^+$ (cells/ml)	594.84 ± 27.473	381.433 ± 29.558 (0.000)*	380.035 ± 27.029 (0.001)*
$CD3^+$ count (cells/ml)	1897.60 ± 205.709	1707.95 ± 167.494 (0.472)	1712.55 ± 149.44 (0.463)
$CD4^+/CD3^+$	0.363 ± 0.121	0.235 ± 0.0153 (0.000)*	0.238 ± 0.0147 (0.000)*
hsCRP (mg/dl)	1.404 ± 0.148	4.822 ± 0.429 (0.000)*	2.649 ± 0.321 (0.005)*
Df		115	131

Table 7: *Comparison of immunologic parameters in HIV infected male and female subjects who were not on antiretroviral therapy with control groups.*

Parameter	Male Control Subjects Mean ± SEM n = 20	Male ART subjects Mean ± SEM n = 26	Male Non-ART subjects Mean ± SEM n = 25
$CD4^+$ (cells/ml)	640.75 ± 43.906	440.28 ± 38.570 (0.000)	363.20 ± 48.191 (0.011)
$CD3^+$ count (cells/ml)	1828.50 ± 107.953	1795.64 ± 190.643 (0.499)	1617.92 ± 249.32 (0.222)
$CD4^+/CD3^+$	0.3705 ± 0.021	0.2164 ± 0.024 (0.000)	0.256 ± 0.020 (0.003)
hsCRP (mg/dl)	1.645 ± 0.248	3.616 ± 0.516 (0.002)	1.32 ± 0.601 (0.337)
Df		44	43
Parameter	**Female Control Subjects Mean ± SEM n = 30**	**Female ART subjects Mean ± SEM n = 41**	**Female Non-ART subjects Mean ± SEM n = 62**
$CD4^+$ (cells/ml)	564.23 ± 34.679	389.146 ± 38.570 (0.002)	355.742 ± 29.73 (0.000)
$CD3^+$ count (cells/ml)	1943.66 ± 337.480	1596.44 ± 249.322 (0.103)	1750.70 ± 204.008 (0.609)
$CD4^+/CD3^+$	0.361 ± 0.0146	0.244 ± 0.0201 (0.000)	0.231 ± 0.017 (0.000)
hsCRP (mg/dl)	1.243 ± 0.181	5.573 ± 0.601 (0.000)	3.185 ± 0.423 (0.002)
Df		69	90

Table 8: *Comparison of immunologic parameters in HIV subjects on therapy and who were not with HIV naïve control subjects.*

Parameter	Male ART subjects Mean ± SEM (n = 26)	Male Non-ART subjects Mean ± SEM (n = 25)
$CD4^+$ (cells/ml)	440.28 ± 38.570	363.20 ± 48.191 (0.316)
$CD3^+$ count (cells/ml)	1795.64 ± 190.643	1617.92 ± 249.32 (0.218)
$CD4^+/CD3^+$	0.2164 ± 0.024	0.256 ± 0.020 (0.214)
hsCRP (mg/dl)	3.616 ± 0.516	1.32 ± 0.601 (0.000)
df	49	
Parameter	**Female ART subjects Mean ± SEM (n = 41)**	**Female Non-ART subjects Mean ± SEM (n = 62)**
$CD4^+$ (cells/ml)	389.146 ± 38.570	355.742 ± 29.73 (0.461)
$CD3^+$ count (cells/ml)	1596.44 ± 249.322	1750.70 ± 204.008 (0.230)
$CD4^+/CD3^+$	0.244 ± 0.0201	0.231 ± 0.017 (0.428)
hsCRP (mg/dl)	5.573 ± 0.601	3.185 ± 0.423 (0.001)
df	101	

Table 9: *Comparison of immunologic parameters in HIV subjects on antiretroviral therapy with HIV subjects who were not on therapy.*

Evaluation of renal function in the study population

Parameter	Control Subjects Mean ± SEM n = 50	ART subjects Mean ± SEM n = 67	Non-ART subjects Mean ± SEM n = 87
Age (year)	31.04 ± 1.269	35.223 ± 1.059 (0.012)	34.874 ± 0.926 (0.015)
Weight (kg)	67.72 ± 1.503	62.075 ± 1.358 (0.007)	58.724 ± 1.341 (0.000)
Cr (mg/dl)	0.682 ± 0.012	0.732 ± 0.0315 (0.189)	0.783 ± 0.0957 (0.424)
CrCl (mg/dl)	149.47 ± 2.979	131.376 ± 4.511 (0.002)	128.722 ± 4.110 (0.001)
Df		115	131

Table 10: *Comparisons of renal function parameters in HIV infected male and female subjects who were and who were not on ART with male and female control groups.*

Key: Cr = Creatinine; CrCl = Creatinine Clearance.

Parameter	Male Control Subjects Mean ± SEM n = 20	Male ART subjects Mean ± SEM n = 26	Male Non-ART subjects Mean ± SEM n = 25
Age (year)	35.950 ± 2.305	35.16 ± 2.220 (0.850)	35.76 ± 1.095 (0.955)
Weight (kg)	75.90 ± 1.620	60.72 ± 2.205 (0.000)	61.08 ± 1.641 (0.000)
Cr (mg/dl)	0.738 ± 0.012	0.81 ± 0.0683	0.747 ± 0.029 (0.741)
CrCl (mg/dl)	147.34 ± 3.386	117.630 ± 6.273	119.059 ± 5.897 (0.000)
Df		44	43

Parameter	Female Control Subjects Mean ± SEM n = 30	Female ART subjects Mean ± SEM n = 41	Female Non-ART subjects Mean ± SEM n = 62
Age (year)	27.766 ± 1.136	35.146 ± 1.095 (0.000)	34.516 ± 0.0897 (0.000)
Weight (kg)	62.266 ± 1.627	62.219 ± 1.641 (0.860)	57.77 ± 1.591 (0.082)
Cr (mg/dl)	0.644 ± 0.0150	0.6854 ± 0.028 (0.245)	0.798 ± 0.134 (0.429)
CrCl (mg/dl)	150.88 ± 4.452	138.543 ± 5.897 (0.171)	132.62 ± 5.336 (0.030)
df		69	90

Table 11: *Comparison of renal function parameters in HIV subjects on therapy and who were not with HIV negative subjects.*

Parameter	Male ART subjects Mean ± SEM n = 26	Male Non-ART subjects Mean ± SEM n =25
Age (year)	35.16 ± 2.220	35.76 ± 1.095 (0.897)
Weight (kg)	60.72 ± 2.205	61.08 ± 1.641 (0.999)
Cr (mg/dl)	0.81 ± 0.0683	0.747 ± 0.029 (0.419)
CrCl (mg/dl)	117.630 ± 6.273	119.059 ± 5.897 (0.891)
df	49	
Parameter	**Female ART subjects Mean ± SEM n = 41**	**Female Non-ART subjects Mean ± SEM n = 62**
Age (year)	35.146 ± 1.095	34.516 ± 0.0897 (0.658)
Weight (kg)	62.219 ± 1.641	57.77 ± 1.591 (0.045)
Cr (mg/dl)	0.6854 ± 0.028	0.798 ± 0.134 (0.504)
CrCl (mg/dl)	138.543 ± 5.897	132.62 ± 5.336 (0.376)
df	101	

Table 12: *Comparison of renal function parameters in male and female HIV subjects on therapy with male and female HIV subjects who were not on therapy.*

Evaluation of haematological factor in the study population

Parameter	Male Control subjects Mean ± SEM (n = 20)	Male ART subjects Mean ± SEM (n = 26)	Male Non-ART subjects Mean ± SEM (n = 25)
WBC $x10^9$/L	5.460 ± 0.350	5.315 ± 0.333 (0.769)	4.724 ± 0.265 (0.095)
PLT $x10^9$/L	220.000 ± 10.883	249.461 ± 11.78 (0.081)	150.00 ± 5.426 (0.000)*
Hb (g/dl)	14.105 ± 0.226	14.138 ± 0.166 (0.983)	11.044 ± 0.585 (0.000)*
PCV (%)	41.515 ± 0.668	42.462 ± 0.647 (0.321)	34.932 ± 1.084 (0.000)*
MCHC (g/dl)	34.010 ± 0.298	33.288 ± 0.224 (0.055)	33.02 ± 0.331 (0.036)
NEU $x10^9$/L	49.255 ± 1.7777	47.473 ± 1.542 (0.607)	30.32 ± 1.498 (0.000)*
LYM $x10^9$/L	40.59 ± 1.624	34.000 ± 1.338 (0.003)	50.672 ± 1.488 (0.000)*
MON $x10^9$/L	12.76 ± 0.981	18.0577 ± 1.028 (0.001)	19.76 ± 0.981 (0.000)*
Df		44	43

Parameter	Female Control subjects Mean ± SEM (n = 30)	Female ART subjects Mean ± SEM (n = 41)	Female Non-ART subjects Mean ± SEM (n = 62)
WBC x10^9/L	5.09 ± 0.164	5.168 ± 0.181 (0.760)	4.916 ± 0.178 (0.537)
PLT x10^9/L	227.533 ± 9.31	235.804 ± 10.183 (0.566)	172.503 ± 7.04 (0.000)*
Hb (g/dl)	12.54 ± 0.122	12.912 ± 0.143 (0.064)	10.358 ± 0.211 (0.000)*
PCV (%)	37.38 ± 0.484	38.053 ± 0.948 (0.573)	31.551 ± 0.614 (0.000)*
MCHC (g/dl)	33.35 ± 0.266	33.117 ± 0.21 (0.489)	32.853 ± 0.201 (0.151)
NEU x10^9/L	50.65 ± 1.877	46.83 ± 1.542 (0.119)	34.350 ± 1.108 (0.000)*
LYM x10^9/L	36.32 ± 2.02	39.16 ± 1.522 (0.256)	50.103 ± 0.986 (0.000)*
MON x10^9/L	11.29 ± 0.839	14.68 ± 0.675 (0.002)	15.98 ± 0.698 (0.000)*
df		69	90

Table 13: *Comparison of haematologic factors in HIV infected subjects who were and who were not on therapy with HIV negative subjects.*

Key: WBC = White Blood Cell Count; NEU = Neutrophil; Hb = Haemoglobin; LYM = Lymphocytes; PCV = Packed Cell Volume; PLT = Platelet; MCHC = Mean Cell Haemoglobin Concentration; n = Number of Samples; df = Degree of Freedom.

Parameter	Male ART subjects Mean ± SEM (n = 26)	Male Non-ART subjects Mean ± SEM (n = 25)
WBC x10^9/L	5.315 ± 0.333	4.724 ± 0.265 (0.173)
PLT x10^9/L	249.461 ± 11.78	150.00 ± 5.426 (0.000)*
Hb (g/dl)	14.138 ± 0.166	11.044 ± 0.585 (0.000)*
PCV (%)	42.462 ± 0.647	34.932 ± 1.084 (0.000)*
MCHC (g/dl)	33.288 ± 0.224	33.02 ± 0.331 (0.503)
NEU x10^9/L	47.473 ± 1.542	30.32 ± 1.498 (0.000)*
LYM x10^9/L	34.000 ± 1.338	50.672 ± 1.488 (0.000)*
MON x10^9/L	18.0577 ± 1.028	19.76 ± 0.981 (0.658)
df	49	
Parameter	**Female ART subjects Mean ± SEM (n = 41)**	**Female Non-ART subjects Mean ± SEM (n = 62)**
WBC x10^9/L	5.168 ± 0.181	4.916 ± 0.178 (0.342)
PLT x10^9/L	235.804 ± 10.18	172.503 ± 7.04 (0.000)*
Hb (g/dl)	12.912 ± 0.143	10.358 ± 0.211 (0.000)*
PCV (%)	38.053 ± 0.948	31.551 ± 0.614 (0.000)*
MCHC (g/dl)	33.117 ± 0.21	32.853 ± 0.201 (0.382)
NEU x10^9/L	46.83 ± 1.542	34.350 ± 1.108 (0.000)*
LYM x10^9/L	39.16 ± 1.522	50.103 ± 0.986 (0.000)*
MON x10^9/L	14.68 ± 0.675	15.98 ± 0.698 (0.240)
n	41	62
df	101	

Table 14: *Comparison of haemoglobin factors in HIV subjects on therapy with their counterpart who were not on therapy.*

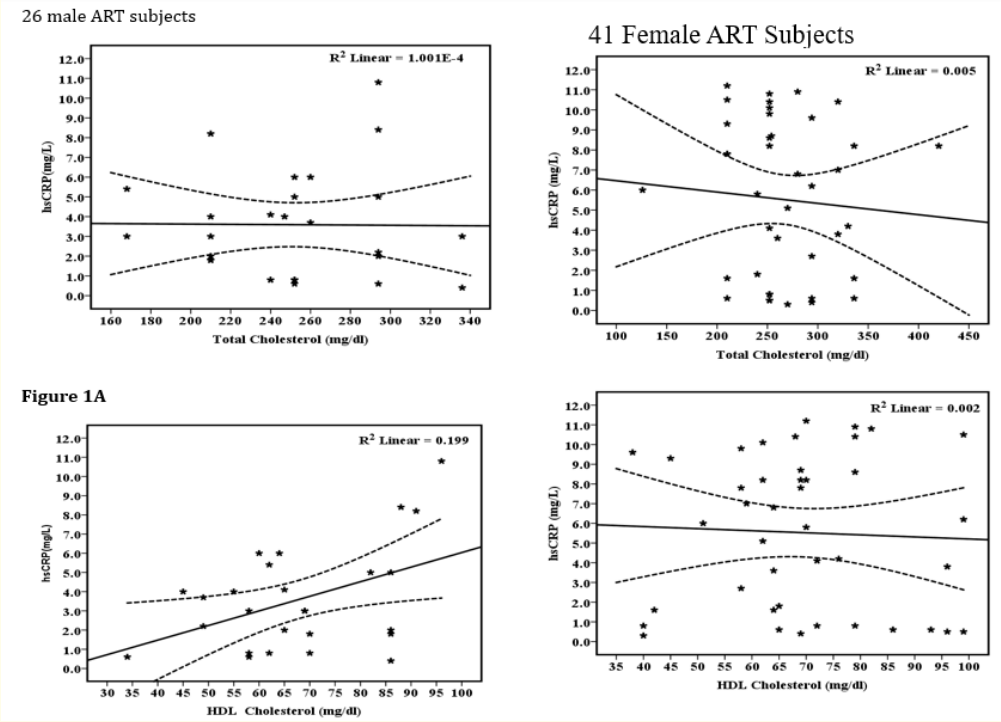
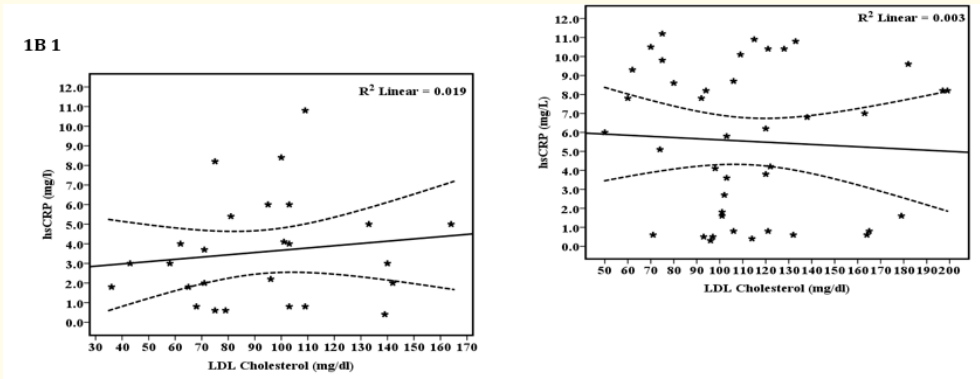
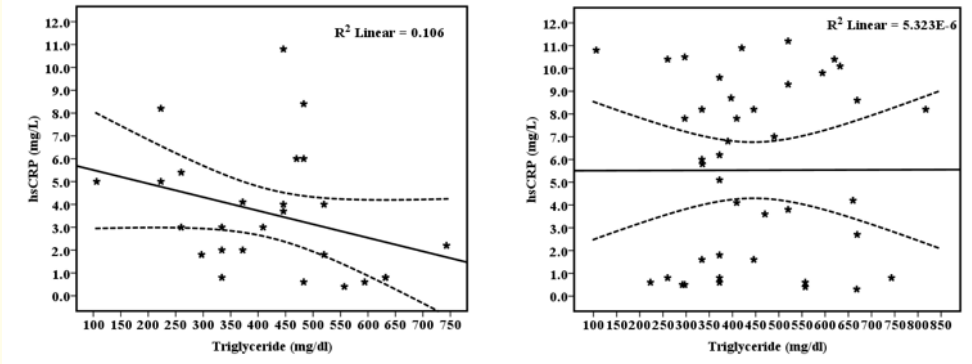


Figure 1A

1B 1



1C 1



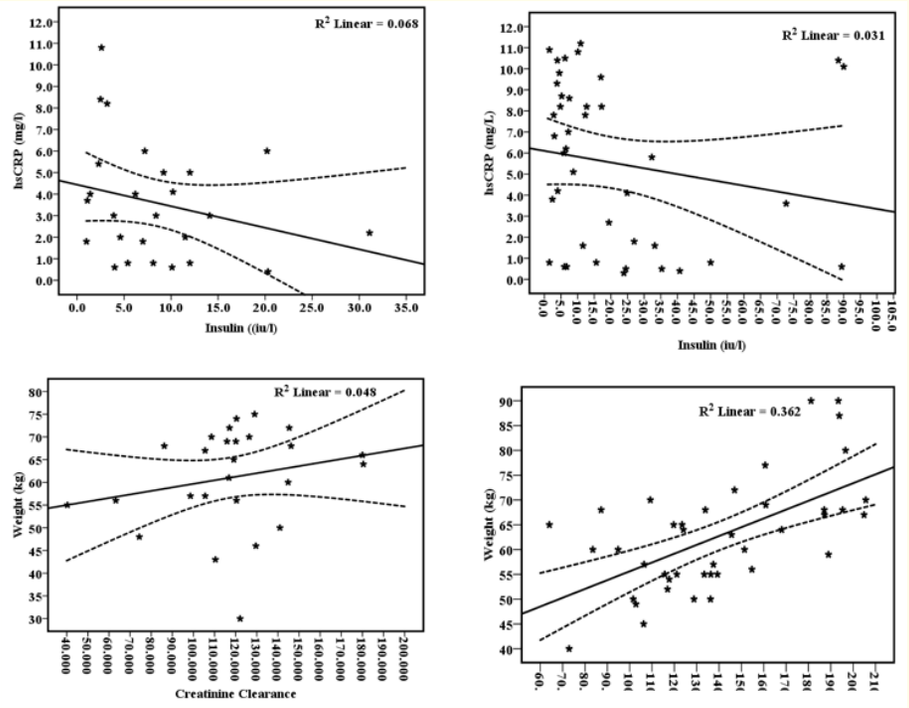


Figure 1: *Association of total cholesterol, HDL, LDL, triglyceride, insulin and creatinine clearance with hsCRP in 26 male and 41 female ART subjects (Regression coleration analysis). Corelation insignificant at the 0.05 level (2-tailed) and 0.01 level (2-tailed).*

Discussions

A total of 154 HIV seropositive subjects seen at the HIV laboratory of the Abia State University Teaching Hospital, Aba, were enrolled into the study. They were stratified into four groups. Group 1 and 2 were made up of 25 males and 62 females HIV seropositive subjects who were not yet on antiretroviral therapy, while group 3 and 4 are made up of 26 males and 41 females who were already on routine antiretroviral therapy (a combination of Lamivudine 150 mg and Zidovudine 300 mg and Nevirapine 200 mg) at least for the past 12 months. The age range of the study subjects population was 15 to 55 years. Also, a total of 50 HIV seronegative subjects, made up of 20 males and 30 females participated in the study. They served as controls. The age range was 18 to 50 years.

The results arising from the analysis of the data generated from the study were presented in the tables above, under the following titles: Cardiovascular, metabolic, immunologic, renal function and haematologic markers. Each of the classification was covered in all the groups of the study population. Table 1 to 5 above showed the results of the evaluation of cardiovascular markers in the various groups of the study population.

Table 1 showed the comparison of cardiovascular markers of the HIV seronegative subjects that served as control 1 (males and females) with HIV seropositive male and female subjects who were on antiretroviral therapy (ART) and those who were not (non-ART). The results showed that the mean ± SEM level of total cholesterol in ART subjects was higher but not statistically compared with control subjects (260.702 ± 5.795 mg/dl vs 252.345 ± 8.535 mg/dl), while the serum total cholesterol mean ± SEM level (208.34 ± 4.193 mg) of non-ART subjects was significantly lower compared with control subjects ($p < 0.001$). The ART subjects mean ± SEM serum levels of LDL-cholesterol (107.00 ± 4.132 mg/dl) was slightly higher compared with control subjects (106.126 ± 6.267 mg/dl). The reverse was the case with non-ART subjects.

The results also showed that serum mean ± SEM levels of HDL cholesterol in ART subjects and non-ART subjects were both non significantly lower compared with control subjects. On the other hand, the mean ± SEM serum levels of total cholesterol - HDL cholesterol ration in both ART and Non-ART subjects did not show any statistically significant difference compared with the control subjects.

However, the mean ± SEM level of triglyceride of ART and Non-ART subjects were remarkably higher compared with control subjects ($P < 0.001$). Also, the serum levels of high sensitivity C-reactive protein were higher in ART subjects (4.822 ± 0.429 mg/dl) and non-ART subjects (2.649 ± 0.208 mg/dl) compared with the control subjects (1.404 ± 0.148 mg/dl) $P < 0.001$ x $P < 0.005$. The hsCRP serum level elevation is suggestive of both immunologic inflammation and cardiovascular atherogenic disorder. The trend of serum levels of lipids profile of this study agreed with the reports of some authors with minor discordants in few areas. The results agreed with the report of Grunfield., *et al.* [14]. They reported decreased serum levels of total cholesterol, HDL-cholesterol, LDL-cholesterol ad elevated serum triglyceride in HIV infection. However, they are of the opinion that decreased serum total cholesterol appear primarily in subjects with AIDS defining illness.

This is at variance with increased serum total cholesterol recorded in HIV infection in this stage. However, the results of this study agreed with the reports of some other authorities. Currier [4] reported that HIV infection is associated with decreased serum levels of total cholesterol, HDL-cholesterol, moderate reduction of LDL-cholesterol and elevated serum levels of triglyceride. Currier [4] also reported a similar lipid pattern in HIV infection. They submitted that sero-conversion was associated with a mean decrease in total cholesterol levels about 15% including LDL and HDL-cholesterols. Stein [15] also reported that untreated HIV infection is associated with decreased total cholesterol and high-density lipoprotein cholesterol and with increased triglycerides and the presence of small dense low-density lipoprotein (LDL) particles.

The mechanism of these lipid abnormalities remain uncertain, especially the picture of hypertriglyceridemia, which is present even among HIV subjects with relatively preserved CD4+ cell count levels. Stein [15] suggested that the high levels of triglycerides were due to, in part, reduced clearance of VLDL cholesterol from the circulation, but the precise mechanism by which HIV infection led to this change was not well explained. Other scientist suggested that one or more of the circulatory cytokines was responsible for these lipid changes [9].

However, from the results of this study, lipid changes in HIV-infection may probably be due to immunological changes. HIV infection triggers high level production of immunoglobulins (antibodies) against the virus, this may lead to elevations in interferon alpha, c-reactive protein an interleukin. Constant production of antibodies by the immune system may lead to production of non-immunocompetent antibodies to fight the virus. This places a high demand on the body's stored cholesterol that may deplete the serum level. On the other hand, the mass production of antibodies by the immune system may increase the triglyceride serum level.

The summary of the serum levels of the cardiovascular markers in ART subjects as shown in table 1 showed significantly elevated serum levels of total cholesterol (260.702 ± 5.795 mg/dl), triglyceride (435.866 ± 18.565 mg/dl) and high sensitivity c-reactive protein (4.822 ± 0.429 mg/dl) compared with the control subjects ($P < 0.001$). Non-significant elevation is serum levels of LDL-cholesterol and reduction in HDL-cholesterol of ART subjects were rewarded compared with the control subjects.

The results of the lipid profile of ART subjects of this study agreed with the report of Graeme., *et al.* [16]. They reported similar results in HIV-infected subjects receiving ART treatment. They concluded that the risk for cardiovascular disease may be significantly greater in the subjects than that of the general population and may increase with each year of ART response.

Stein [15] with a similar lipid profile result, but hsCRP not included also suggested that the risk of myocardial infarction was higher among subjects receiving ART and particularly the use of protease inhibitors. Other authors who reported increased atherogenic lipid levels in HIV subjects receiving ART include: Frii-Moller., *et al*. [17] and Passalaris., *et al*. [18]. They all suggested the possibility of long-term risk of atherosclerotic cardiovascular events for ART subjects who experience increases in atherogenic serum lipids, insulin resistance, dysglycemia and body fat redistribution. However, some other scientists were of the contrary opinion. Bozzette., *et al*. [19] reported that the rates of hospital admission for cardiovascular disease declined after the introduction of antiretroviral therapy. He maintained

that the number of deaths for cardiovascular causes did not increase and that specific classes of antiretroviral drugs were not related to cardiovascular risk during a mean follow up to 15 months. Bozzette., *et al*. [19] in the report did not attribute increases in atherogenic serum lipids to antiretroviral drugs, rather to HIV infection. He reported that multicenter AIDS cohort study has helped to illuminate the role of HIV infection in the pathogenesis of hyperlipidemia in ART subjects. He said after sero-conversion, subjects experienced reductions in total cholesterol, LDL- and HDL-cholesterols compared with their pre-conversion levels. When they started antiretroviral therapy, their total cholesterol, LDL-cholesterol and triglyceride levels, but not their HDL-cholesterol levels promptly returned toward their pre-conversion levels. He maintained that the early increases in lipid levels from baseline commonly observed in studies of treatment naïve subjects may not represent true elevations, but rather a return to those subjects normal values, Dube., *et al*. [20] also shared this school of thought. They therefore did not completely agree that ART except protease inhibitor is associated with risk of future cardiovascular event.

However, this study is of the view that increased atherogenic serum lipids may be due to both HIV-infection and antiretroviral drug. It is important to keep in mind some effects of HIV-infection itself when considering lipid changes, like increased inflammation to the immune system which reflected in the results of this study in the form of elevated serum levels of triglycerides and high sensitivity c-reactive protein. Also, antiretroviral drug may increase inflammation or stress in the process of boosting the immune system, which may the serum lipid levels. It is possible that in some circumstances, lipid changes, especially increases in total and LDL cholesterol may not be a toxicity of medication per se, but rather a reversal of the effect of HIV infection. This is particularly relevant given that information is rarely available on the subjects lipid profile before the acquisition of HIV infection or even before the initiation of therapy as was the case in this study. Thus, it is not possible to know what that patient's total and LDL cholesterol would have been without HIV infection. A significant proportion of HIV negative individuals have elevated total and LDL cholesterol, so it is conceivable that a considerable proportion of the dyslipidemia seen in HIV subjects on ART represent a "return to normal" rather than a toxicity of medication.

In contrast, the decrease in HDL-cholesterol associated with HIV infection was not reversed with treatment. The fact that increases in total cholesterol may to some extent, represent "Normalization" does not make the problem any less important or reduce the need to consider lipid lowering medications. However, it does suggest that antiretroviral HIV therapy is not the sole cause of dyslipidemia.

Table 2 showed the comparison of HIV seropositive male subjects who were on antiretroviral therapy and who were not compared with HIV seronegative male subjects. The results followed almost similar pattern with results in table 1 except minor differences in the levels of significant differences. Triglyceride mean ± SEM levels in male on ART (420.36 ± 30.184 mg/dl) and non-ART (398.64 ± 23.692 mg/dl) were both significantly higher compared with the control subjects (164.25 ± 11.193 mg/dl) ($P < 0.001$). Also, male ARTS subjects had higher serum levels of total cholesterol (251.160 ± 9.106 mg/dl) and hsCRP (3.616 ± 0.516 mg/dl) compared with the control subjects ($P < 0.002$). The reverse was the case with male non-ART subjects, with no significant difference. Table 2 showed the comparison of cardiovascular risk markers in HIV infected female subjects on ART and those who were not compared with HIV seronegative female subjects. The results followed a similar pattern with that of their male counterpart.

Tables 3 showed the comparison of the serum levels of cardiovascular markers in HIV seropositive subjects who were on antiretroviral therapy with HIV seropositive subjects who were not on therapy, for both male and female subjects respectively. Subjects on antiretroviral therapy had higher serum levels of cardiovascular markers compared with those who were not. Significant differences were recorded in hsCRP values for both male and female groups.

Conclusively, the cause of dyslipidemia seen in some HIV infected subjects receiving antiretroviral therapy may be multifunctional. It could be a return of normal of subjects' lipid level before initiating therapy, inflammatory activity of the virus as supported by elevated value of hsCRP in this study of effects of medication.

The results of metabolic markers evaluated in this study were presented in table 4-6. Table 4 showed comparison of metabolic markers in HIV seropositive male and female subjects who were on antiretroviral therapy (ART) and those who were not (non-ART) with control subjects (HIV seronegative subjects). The mean ± SEM serum levels of glucose and insulin in ART subjects were significantly higher compared with the control subjects ($P < 0.001$). Similar results were also seen in non-ART subjects, however, only serum glucose level was significantly recorded in this work.

Hyperinsulinemia recorded in this work agreed with reports of some researchers. Hadigan [21] reported hyperinsulinemia in HIV infected subjects on therapy. Murala., *et al*. [22] reported hyperinsulinemia in HIV subjects receiving antiretroviral and attributed the causes to medication, dyslipidemia and inflammation. Hyperinsulinemia is indicative of insulin resistance. Potentially, it leads to the development of type II diabetes mellitus. It is associated with an atherogenic lipid profile and impaired thrombolysis and contributes independently to an increased risk of cardiovascular disease. In the early stages of insulin resistance, insulin levels rise to compensate for resistance, assuring that blood glucose levels remain normal. That explains the normal glucose level recorded in this study amongst ART subjects and non-ART subjects. Over time, pancreatic insulin production may decrease and fasting hyperglycemia and diabetes result.

The exact pathogenesis of hyperinsulinemia (insulin resistance) revealed in this study is unknown. However, it may arise secondary to direct effects antiretroviral medications on insulin-mediated whole body glucose uptake. Any adverse effects on glucose transporter (GLUT4) may cause a rapid and reversible dose-dependent decrease in insulin-stimulated glucose uptake by the cells. Inflammation may play some roles. Adipose tissue macrophages which accumulate in HIV infection are capable of secreting proinflammatory cytokines. In addition, cytokines such as tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6) can be released from adipose tissue. They are known to result in changes in body composition. TNFα impairs the action of insulin while IL-6 increases insulin resistance. Also, low concentrations of leptin and adiponectin are associated with HIV lipodystrophy and they are suggestive of insulin resistance.

The electrolytes results in table 4 showed that all the electrolytes serum levels were non-significantly higher in ART subjects and lower in non-ART subjects compared with the control subjects. The decreased levels recorded in HIV infected subjects who have not initiated antiretroviral therapy may be due to the effect of the virus not only on the electrolytes but also on water homeostasis. Moderate hyponatremia was in mean ± SEM sodium serum level of non-ART subjects (135.839 ± 0.460 mmol/L) with corresponding decreased serum chloride. The results agreed with the reports of Carl., *et al*. [23]. The moderate hyponatremia in this setting may be depletional hyponatremia rather than dilutional. Probably caused by extrarenal loss of Na^+ in excess of H_2O (extracellular fluid) from the gastrointestinal tract, as may be seen in some HIV infected subjects that manifest clinical diarrhea. In most of these subjects, hypovolemia is apparent in the physical examination with clinical picture of orthostatic hypotension, tachycardia and decreased skin turgor.

Table 5 showed the comparison of metabolic markers (except the aminotransferase) in HIV seropositive male and female subjects and antiretroviral therapy and those who were not compared with their respective male and female control subjects. The results followed a similar pattern with results in table 4. The results in table 6 showed the variations of metabolic markers levels in HIV seropositive male and female subjects who were not on therapy.

The results showed that in both genders, subjects on antiretroviral therapy recorded non-significant higher serum levels of metabolic markers compared with those who were not on therapy. This is indicative of positive response of the immune system to antiretroviral therapy. On the other hand, the other metabolic markers, Alanine aminotransferase and Aspartate aminotransferase recorded consistent higher serum levels in HIV infected subjects who have not initiated antiretroviral therapy compared with those who were already on therapy. This result is a clear revelation of the effect of HIV infection on metabolic processes. It is also suggestive of the need of immediate therapeutic intervention to help the immune system in the battle against HIV infection.

Table 7-9 above showed the results of immunologic markers evaluated in the various groups of the study population. Table 7 showed the comparison of immunologic markers serum levels of HIV seronegative male and female subjects with HIV seropositive male and female subjects who were on antiretroviral therapy (ART) and those who were not (non-ART). The results showed mean ± SEM CD4+ cell count was significantly higher in control subjects compared with HIV seropositive subjects on antiretroviral therapy and those who were not ($P < 0.001$) respectively. Those lower CD4+ cell count was recorded in HIV seropositive subjects who have not initiated antiretroviral therapy compared to those who were already on therapy. The results of this study agreed with the reports of other investigators. They all agreed that HIV infection causes a reduction in blood CD4+ cell count. While an improvement in CD4+ cell count is a positive indication of response to treatment in HIV infection management [24]. In most HIV care centers in Nigeria, CD4+ cell count form the immunological bases for initiation antiretroviral treatment (CD4+ cell count ≤ 350 cells/ml) with clinical symptoms. It is used for evaluating the progress of treatment as well as one of the criteria for evaluating the progression of the infection to disease state (AIDS). However, viral-load testing is more standard tool in HIV management.

Also in table 7, the result of serum levels of high sensitivity c-reactive protein showed that the mean ± SEM of HIV seropositive subjects on antiretroviral therapy (4.822 ± 0.429 mg/dl) and those who were not on therapy (2.649 ± 0.321 mg/dl) were significantly higher compared with the control subjects (1.404 ± 0.1481 mg/dl) ($P < 0.001$ and $P < 0.005$). These findings agreed with the reports of Appay and Sance [25]. They increased serum levels of hsCRP in HIV infection and associated it with inflammation. They submitted that it has a critical role in cardiovascular disease. Coll., *et al*. [26] attributed increased serum level of hsCR to both infection and antiretroviral therapy. They concluded that elevated hsCRP levels suggest that inflammation is relevant to the pathophysiology of metabolic distribution in HIV infected persons on treatment, and may be a useful marker of acute coronary syndrome.

Table 8 showed the comparison of serum levels of immunologic markers in HIV seropositive male and female subjects who were on antiretroviral therapy and those who were not with their HIV seronegative subjects (controls). The results followed the pattern if results in table 7 above. Also, a similar result was revealed in table 9 respectively, which showed comparison of immunologic markers in HIV seropositive male and female subjects on therapy with their respective counterparts who have not initiated antiretroviral therapy. In all, the mean serum levels of CD4+ counts and hsCRP were higher in HIV seropositive subjects and therapy compared with those who have not initiated therapy. The mean serum levels of CD3+ counts and CD4 – CD3 ratio showed discordant in HIV seropositive subjects on therapy and those who were not. Thus, they offered no useful information in this study as immunologic markers.

The results of renal function markers evaluated in this study were presented in table 10 to 12. the result in table 10 compared the renal function makers in HIV seronegative male and female subjects (Control) with HIV seropositive subjects (male and females) on antiretroviral therapy (ART) and those who were not (non-ART). The results showed that mean ± SEM creatinine clearance levels were significantly lower in both HIV seropositive subjects not on therapy (128.722 ± 4.110 ml/mm) and those who were on antiretroviral therapy (131.376 ± 4.511 ml/mm) compared with the subjects (149.47 ± 2.979 ml/mm) $P < 0.001$ and $P < 0.002$. The serum creatinine levels were significantly the reverse of the creatinine clearance results. However, the control subjects were young and weighed more than the HIV seropositive subjects, factors that could have affected the results of this study. On the other hand, the results showed that the serum creatinine clearance values of both HIV seropositive subjects on therapy and those who were not were more within the normal reference values (70 - 150 ml/mm).

Table 11 showed the comparison of renal function markers in HIV seronegative subjects male and female with their respective HIV seropositive male and female subjects on antiretroviral therapy (ART) and those who were not (non-ART). The results were similar to that in table 16 except some discordant in serum levels creatinine amongst HIV seropositive male subjects caused by age and weight differences. In table 11, the mean ± SEM levels of serum creatinine (0.644 ± 0.015 mg/dl) and creatinine clearance (138.543 ± 5.899 mg/dl) of HIV seropositive female on therapy were lower and higher respectively compared to those who were not. The reverse was the case in HIV seropositive male subjects results in table 11, results already given.

The results in table 12 showed comparison of HIV seropositive male subjects on therapy and HIV seropositive female subjects on therapy with their respective counterparts who were not on therapy. The results showed similar pattern to that in the tables discussed above. The results of this study agreed with the reports of [23]. They studied kidney function trends in HIV/AIDS subjects at Nylon District Hospital, Douala, Cameroon. Their findings were indicated that renal function is not affected by the seropositivity status of individuals. On the other hand, a study [24] reported reduced glomerular filtration rate among some HIV/AIDS subjects at Jos University Hospital, Jos. In their study, they used conventional creatinine clearance method. However, this study used Cockroft and Gault formula in calculating the serum creatinine clearance. Also, AIDS subjects were included in their study while this study used HIV subjects.

The results of this study showed moderate reduction in renal function activity in HIV seropositive subjects compared with those who were on antiretroviral therapy but was not indicative of renal pathology while the results of those on therapy did not suggest nephrotoxicity.

Table 13 and 14 showed the results of haematological parameters evaluated in this study. Table 13 showed the comparison of haematological factors in HIV seronegative male subjects (control) with HIV seropositive male subjects on antiretroviral therapy (ART) and those who were not (non-ART). The results showed that ART subjects has significantly higher blood mean ± SEM levels of platelets ($P = 0.08$) and monocyte ($p = 0.001$) compared with the control subjects. While non-significant increased levels of packed cell volume (PCR) and haemoglobin (Hb) were also recorded. On the other hand, blood mean ± SEM level of lymphocytes was significantly higher in male control subjects than male ART subjects. Mean cell haemoglobin concentration (MCHC) and neutrophils were non-significantly higher in control subjects also.

Also in table 13, the comparison of haematological parameters of male control subjects with non-ART subjects, the results showed that non-ART subjects had significantly decreased mean ± SEM blood levels of platelets, HB, neutrophil ($P = 0.001$), moderately reduced WBC count, PCV and MCHC concentrations as well as highly elevated lymphocyte and monocyte ($P = 0.001$) compared with male control subjects. The table 13 showed comparison of haematological factors in female control subjects with female ART subjects and non-ART subjects respectively. The results showed the same trend with their male counterpart.

Table 14 showed the comparison of haematological factors in HIV seropositive male subjects on therapy with those who were not. The results showed significantly decreased blood mean ± SEM blood levels of platelets, Hb, PCV, and neutrophil in non-ART subjects compared with ART subjects ($P < 0.001$) while lymphocyte was significantly increased in non-ART subjects, than in ART subjects ($P = 0.001$). The results in table 14: Comparison of haematological factors in HIV seropositive female subjects on therapy with HIV seropositive subjects who have not initiated therapy. The results reflected the results of table 14.

The revelation of this study shows that untreated HIV infection is associated with anaemia. Anaemia is a common complication of HIV infection with important clinical implications- since it exercises an adverse effect on disease prognosis. The cause of HIV associated anaemia are many and diverse. The viral infection alone activates a cytokine response that is inimical to red blood cell production, while at the same time, predisposing its host through global immunosuppression to a myriad of other infections. These infections can also suppress erythropoietic production. Thrombocytopenia was also identified in untreated HIV-infection. Reduced platelets count portrays blood coagulation problems as well as clotting time defects. The aetiology of this problem is believed to be due to antibody production induced by HIV glycoprotein120 which cross-reacts with platelet GP111a. They shortens platelets survival and induces apoptosis of megakaryocytes [27].

Also revealed in untreated HIV infection was neutropenia - A reduction in the number of neutrophils in the blood. The results agreed with the report of Coyle [28]. The aetiology may be inhibition of granulopoiesis by HIV virus or marrow infiltration by infectious organisms. Agranulocytosis, a clinically significant reduction in neutrophils, has the serious consequence of making individuals

susceptible to bacterial and fungal infections. This is the major cause of opportunistic infections in untreated HIV infection. The results also revealed lymphocytosis amongst HIV infected subjects who have not commenced antiretroviral therapy. This was accompanied by moderate monocytosis. The aetiology may be the HIV virus itself accompanied by other co-infections like tuberculosis, brucellosis, cytomegalovirus or hepatitis A. Haematological abnormalities are probably the commonest complications of infection with HIV. Besides diseases, antiretroviral drug therapy may also be responsible for haematological abnormalities.

From the result of this study, it seemed that changes in serum lipids observed in HIV infection and subjects who were on antiretroviral therapy represent the effects of HIV infection and antiretroviral therapy medication. Also hyperinsulinemia recorded probably represents effects of antiretroviral therapy occasioned by insulin resistance which result in normoglycemia in the short run. Also, hsCRP levels in this study is suggestive of the role of inflammation due to both HIV infection and antiretroviral therapy in future cardiovascular events and the potential hsCRP as a sensitive, non-specific cardiovascular marker.

Finally, haematological abnormalities revealed in this study showed the importance of immediate therapeutic intervention in HIV infection. I therefore conclude that periodical biochemical and haematological monitoring of HIV subjects on routine antiretroviral therapy should be made an imperative treatment strategy to reduce the risk of future cardiovascular and haematological complications.

The changes in lipids observed in subjects receiving antiretroviral therapy seems to be a reversal of the subjects normal value before infection and may not absolutely be a toxicity of medication. This is particularly relevant given that information is rarely available on the subjects lipid profile before the acquisition of HIV infection or even before the initiation of therapy. Thus, it is not possible to know what the subjects lipid profile would have been without HIV infection. The fact that increases in total cholesterol may to some extent represent "normalization" does not make the problem any less important or reduce the need to consider lipid lowering medications. However, it does suggest that antiretroviral HIV therapy is not the sole cause of lipid elevations and emphasizes the importance of other sensitive cardiovascular biomarkers apart from addressing the lifestyle and behavioral issues that can contribute to dyslipidemia. Hence, increased serum levels of high sensitivity c-reactive protein in both subjects with HIV infection and those on therapy is suggestive of the role of inflammation in cardiovascular events.

The metabolic markers comprised, evaluation of serum levels of glucose, insulin, electrolytes and aminotransferases. Hyperinsulinemia was recorded among subjects on antiretroviral therapy which is indicative of insulin resistance.

Insulin resistance has been associated not only with the subsequent development of diabetes mellitus but also with increased cardiovascular risk even in the absence of frank diabetes mellitus. Hence, the non-revelation of diabetes mellitus among HIV subjects receiving antiretroviral therapy does not trivialize the risk associated with hyperinsulinemia. Previously PIs were thought to be etiological in insulin resistance observed in HIV-infected subjects. But the results of this study seemed to have shown that NRTIS and NNRTI exposure may equally lead to insulin resistance. There is therefore the need for research on the impact of specific antiretroviral agent (drug) and its treatment duration on glucose and insulin metabolism.

Conclusion

This study was aimed at evaluating cardiovascular risk factors and metabolic abnormalities in subjects infected with human immunodeficiency virus as well as subjects living with the virus who have initiated treatment at least for the past one year. Essentially, cardiovascular risk factors were evaluated in this study, using serum levels of lipid profile and high sensitivity C-reactive protein. The evaluation of metabolic abnormalities were categorized into metabolic, immunologic, renal function and haematologic parameters. Each of the categories used various biomarkers as indicator for assessment. The study recorded some important revelations. It revealed that human immunodeficiency virus infection is associated with decreased serum levels of total cholesterol, density lipoprotein cholesterol

and elevated triglyceride and high sensitivity c-reactive protein. On the other hand, the trend of serum levels of lipid profile of subjects on antiretroviral therapy showed hypercholesterolemia, hypertriglyceridemia, slight increased low density lipoprotein cholesterol and high-density lipoprotein cholesterol as well as elevated high sensitivity C-reactive protein.

Moderate depletional hyponatremia was also observed among HIV infected subjects who have not initiated therapy with a corresponding decreased serum chloride, probably caused by diarrhoea. The results of the aminotransferase showed that antiretroviral treatment was hepatic protective as the serum levels of the enzymes were within reference for subjects on therapy.

The immunologic markers include CD4 count, CD3 count and high sensitivity c-reactive protein. The results showed that apart from viral load testing, CD4 count is the simplest marker for initiating therapeutic intervention as well as for monitoring of treatment in human immunodeficiency virus infection. The serum levels of high sensitivity c-reactive protein in both subjects with HIV infection and those on therapy revealed that both human immunodeficiency and antiretroviral drugs have inflammatory effects in the subjects, probably on the endothelial cells.

The study revealed that human immunodeficiency virus infection has no pathological effect in the renal function. Maybe renal function complications may result at the disease stage, AIDS. It also showed that the antiretroviral drugs evaluated in this study (NRTI and NNRTI) have no nephrotoxicity effect in the subjects infected with human immunodeficiency virus who are on therapy.

The results of this study revealed that haematological abnormalities are probably the commonest complications of infection with human immunodeficiency virus. It is therefore suggestive that many subjects with human immunodeficiency virus infection at some point or the other manifest these complications and hence requires careful workup. The remarkable haematological complications secondary to human immunodeficiency virus infection recorded in the study include anaemia, thrombocytopenia, neutropenia, and lymphocytosis accompanied by moderate monocytosis. Of special note, is the issue of neutropenia probably due to inhibition of granulopoiesis by human immunodeficiency virus. The clinical implication is agranulocytosis with serious consequence of making individuals susceptible to opportunistic infection. It is therefore recommended that treatment of HIV infection should commence as quickly as possible to commence haematologic complications. Also coordinated periodic haematological testing to subjects should be imperative in HIV infection treatment and management strategy.

Another revelation of this study is the potential diagnostic value of high sensitivity C-reactive protein in subjects with HIV infection and those on treatment in cardiovascular risk and metabolic abnormalities assessment.

The elevated serum levels recorded in HIV infection and the trend toward higher hsCRP in therapy. The values suggest that inflammation is relevant to the pathophysiology of metabolic disturbances in HIV infection and chronically HIV infected persons on treatment, confirm that cardiovascular risk by traditional risk factors and risk of acute coronary syndrome by hsCRP are often discordant in HIV infected persons and that inflammatory markers may be of utility. Hence high sensitivity C-reactive protein is a particularly sensitive marker because it allows and provides early prognostic information in cardiovascular event and metabolic disturbances. However, larger studies are needed to assess the associations between hsCRP and clinical outcomes in this study. This study did not place much importance on gender distinction in the evaluation of the various parameters. However, few variations were noticed between males and females in most of the biomarkers studied.

From the findings of this study, some recommendations may be necessary for better management of HIV infected subjects:

- All health care providers involved in the management of HIV subjects should, as a matter of policy, make periodical monitoring of serum lipids and haematological testing part of HIV infection management strategy.

- Serum insulin should be evaluated at least once in every twelve months in subjects on antiretroviral therapy to monitor the possibility of developing insulin resistance and glucose tolerance.
- Study should be carried out on the effects of antiretroviral agents to know their specific effects on serum lipids and their involvement in metabolic disturbances.

Finally, the findings of this study indicate a need for further study of cardiovascular disturbances in HIV infected populations of African origin. This will help to identify the effects of environment and genetic factors in the pathogenesis of these disorders.

Conflict of Interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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Authors' Contributions

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