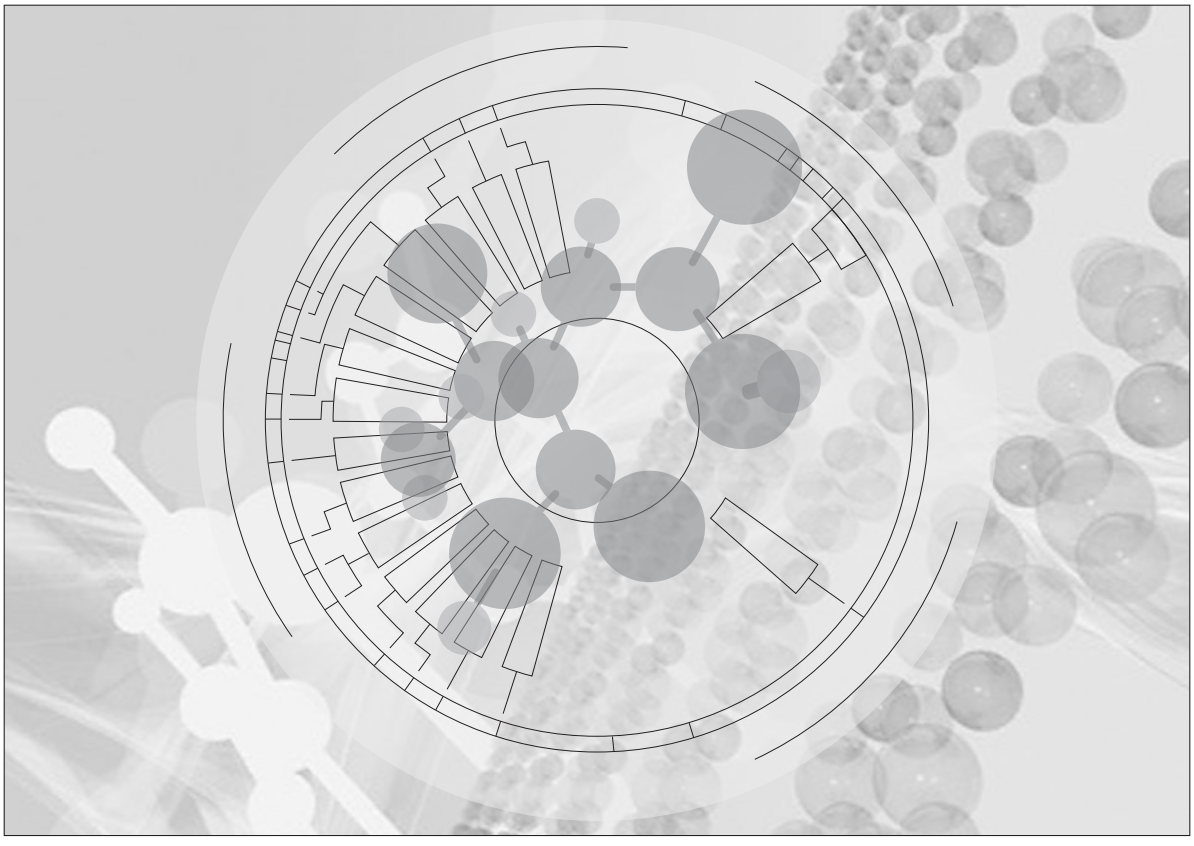

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Effects of HIV Infection and Anti-retroviral Therapy on Cardiovascular Risk Factors

Robert A. Ngala and Klutse Fianko
Department of Molecular Medicine, School of Medical Sciences, Kumasi, Ghana

Corresponding Author: Robert A. Ngala, Department of Molecular Medicine, School of Medical Sciences, Kumasi, Ghana Tel: +233 (0)207722162

ABSTRACT

Several studies show that HIV infection and highly active anti-retroviral therapy increases the risk of patient development of cardiovascular diseases. The increased cardiovascular disease risk factors such as total cholesterol, low density hipoproteins, hypertension and the pathogenesis of HIV infection increase the risk of cardiovascular disease. This study shows the effect of HIV infection and HAART on lipid metabolism and hypertension; the cardiovascular risk factors. Overnight fasted blood samples were drawn from the median cubital vein on the anterior forearm into plain and fluoride oxalate tubes. The serum from the plain tubes was used to estimate the lipid profile:total cholesterol, High density lipoprotein cholesterol, low density lipoprotein and triglycerides and liver function diagnostic enzymes on an autoanalyser. Haemoglobin concentration was determined from the anticoagulated blood and Cluster of differentiation CD_4 was done with Becton Dickinson FACSCount®. The plasma from the fluoridated anticoagulated blood was used to estimate fasting blood glucose. Systolic and diastolic blood pressures were measured with a mercury sphygmomanometer. Markers of cardiovascular diseases, total cholesterol, low density lipoprotein, diastolic and systolic blood pressures were significantly ($p<0.001$) elevated. Aspartate amino transferase and Alanine amino transferase were significantly ($p<0.0009$) reduced in HAART- experienced patients. The significantly increased ($p<0.001$) total cholesterol, low density lipoproteins and decreased ($p<0.05$) high density lipoprotein are indicators of cardiovascular risk. Diastolic and systolic blood pressures were significantly ($p<0.001$) positively correlated to the duration of HAART. Some combinations of highly active antiretroviral drugs were cardio protective at least in the short run.

Key words: Very low density lipoprotein, HAART, hypertension, cardiovascular disease

INTRODUCTION

Several studies show that HIV-infected patients may be at an increased risk for the development of cardiovascular disease (CVD) (Boccara, 2008; Stein *et al*., 2008; Farrugia *et al*., 2009). Cardiovascular risk factors, HIV infection and antiretroviral therapy (ART), all increase the risk of cardiovascular diseases (Friis-Moller *et al*., 2007). Highly active anti-retroviral therapy, generally consists of a combination of nucleoside analog reverse transcriptase inhibitors (NRTI) plus a Protease Inhibitor (PI) and Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI) (Young, 2005). Although, different antiretroviral drugs show different metabolic defects, treatment with highly active anti-retroviral therapy is known to increase cardiovascular risk factors. These

factors include hyperlipidaemia, hypertriglycaeridemia, lipodystrophy, hyperglycaemia and increased insulin resistance (Penzak and Chuck, 2000; Dube *et al.*, 2003). Low levels of Total Cholesterol (TC), high-density lipoprotein cholesterol (HDL) are also known to be associated with chronic HIV infection. Dyslipidaemias are known causes of atherogenesis and atherosclerotic related diseases (Wanke, 1999). These disorders are associated with increased risk of cardiovascular diseases which have become the main cause of morbidity and mortality in HIV-infected patients (Barbaro, 2006; Leclercq and Blanc, 2006; Morse and Kovacs, 2006). Studies among HIV-1-infected patients on HAART showed increased levels of apoB and apoC-III and decreased levels of apoE lipoproteins (Lenhard *et al.*, 2000; Bonnet *et al.*, 2001; Mooser and Carr, 2001; Fauvel *et al.*, 2001). This type of atherogenic lipid profile is likely to increase the risk of cardiovascular complications including myocardial infarction and premature atherosclerosis (Mehta and Reilly, 2005; Carr, 2003).

Although, HIV-1 infection is associated with an atherogenic lipid profile, the use of PI-containing highly active anti-retroviral drugs, particularly ritonavir (RTV) and lopinavir/ritonavir (LPV/r, Kaletra), further aggravate these lipid abnormalities (Badiou *et al.*, 2003; Carpentier *et al.*, 2005; Montes *et al.*, 2005). However, some researchers argue against the link between HAART and coronary heart disease (CAD) based on some designed flaws. These designs, they say do not distinguish between the effects of HIV infection from those of antiretroviral therapy. They do not also distinguish between the effects of the duration of HIV infection and the presence of immunological disturbances and the effects of other co-infections. Also atherosclerosis takes decades to develop and that even if the rate of the atherogenic effect of HIV infection and antiretroviral therapy were doubled, it would take at least 10 years for these effects to manifest, but these studies had very short follow ups (Fichtenbaum, 2003). The Veterans Affairs Study supports these arguments. The study showed no significant increase in cardiovascular or cerebrovascular events in patients treated with HAART or protease inhibitors (PIs) compared with age adjusted uninfected population (Bozzette *et al.*, 2003). In contrast, a French Hospital Data Base, showed that, rates of myocardial infarctions were increased in subjects on long term treatment with protease inhibitors (Mary-Krause *et al.*, 2003). Several theories have been postulated to explain the possible mechanisms for protease-inhibitor-induced endothelial dysfunction. This dysfunction appears to be effected through reduced nitric oxide production or release, on the evidence of both clinical (Shankar *et al.*, 2005) and experimental models. Specific mechanisms include; reduced expression of endothelial nitric oxide synthase (Fu *et al.*, 2005) and increased reactive oxygen species concentration (Baliga *et al.*, 2004), which seems to catalyze atherogenic activity of the lipids.

Atherosclerosis, the main factor for the development of CAD is a complex inflammatory process, marked by the presence of lymphocytes, foam macrophages, enhanced expression of adhesion molecules, proliferation of smooth muscle cells and, the maturation of lipid loaded plaques (Fichtenbaum, 2003). Several other well-described risk factors are associated with CAD, including a family history of premature atherosclerosis, diabetes mellitus, hypertension, cigarette smoking, obesity and physical inactivity (Bertoli *et al.*, 2003).

Several mechanisms of inflammation have been postulated to explain the link between HIV infection and cardiovascular risk. Endothelial cells are known to be involved in the aetiology of atherosclerosis associated with HIV infection through inflammation (De Gaetano Donati *et al.*, 2004). High concentrations of Willebrand factor antigen have been reported in HIV disease, particularly in patients with a high viral load or advanced disease state. Plasma concentrations of

inflammation markers including adhesion molecules, intercellular adhesion molecule-1 and vascular adhesion molecule-1 are raised in HIV patients and are directly related to the level of inflammation (Chi *et al.*, 2000). Increased rates of inflammation are associated with higher carotid intima-media thickness (Hsue *et al.*, 2004). In recent times, a study found that untreated HIV infection was associated with high level of interleukin 6 (IL-6) and D dimer and that these biomarkers were associated (Ho and Hsue, 2009) with all causes of mortality and to a lesser extent cardiovascular disease. IL-6 is increased by infection and inflammation and has been shown to be an independent predictor of mortality in angina (Calmy *et al.*, 2009). HIV infected individuals also have higher high sensitivity C-reactive protein (hsCRP) values and T cell activation compared with uninfected individuals (Hsue *et al.*, 2004). The hsCRP, a biomarker of inflammation is also an independently known predictor of cardiovascular activities. hsCRP is raised in both HAART and HAART-naïve patients (Mangili *et al.*, 2011). This may imply that HIV infection alone can induce cardiovascular diseases. This study was aimed at showing the effects of HIV infection and HAART on cardiovascular risk factors such as total cholesterol, low density lipoproteins, hypertension and their correlation to cardiovascular diseases in HIV-infected patients.

MATERIALS AND METHODS

The study was carried out at Kumasi South Hospital under the National Aids Control Programme. All procedures were approved by the Committee on Human Research Publication and Ethics of School of Medical Sciences, KNUST (CHRPE/Student/113/09). A written informed consent form was completed by all the participants who were recruited into the study after the study was explained in a language they understand. Pre-tested questionnaires were used to record information of the participants. Information on demography, lifestyle, physical examination and anthropometric measurements were taken.

Study design: The study involved a total of 305 HIV-infected patients, one hundred and sixty four on highly active antiretroviral therapy for at least six months and classified as HAART experienced and 141 HAART-naive patients constituted HIV-positive patients, not on HAART and whose CD_4 was not below the critical value of 320 cell mL^{-1}).

Antiretroviral drugs used include: Stavudine, lamivudine, efavirenz, zidovudine and nevirapine.

All the HAART experienced participants involved in the study used a combination of these drugs, grouped under NRTI consisting:stavudine, lamivudine and zidovudine and NNRTI consisting; of nevirapine and efavirenz. The combination consisted of a stavudine based lamivudine with either nevirapine or efavirenz and a zidovudine based lamivudine combined with either nevirapine or efavirenz. Participants with opportunistic infections, hypertension or cardiac disease before HAART were excluded.

Sample preparation and biochemical assay: Overnight fasted blood samples were drawn from the median cubital vein on the anterior forearm into plain and fluoride oxalate tubes (to prevent glycolysis), BD vacutainer®, (BD, Plymouth, PL6 7BP. UK). The clotted blood was centrifuged at 2000 rpm (Zentrifugen, D-78532, Tuttlingen, Germany) for 5 minutes to separate out the serum. The serum was used to estimate the lipid profile: Total cholesterol, High density lipoprotein cholesterol, low density lipoprotein and triglycerides were estimated with Selectra Junior (Vital Scientific, N.V. Netherlands) automated assay. Inter assay coefficient of variation (2.3 and 2.1% for low and high total cholesterol controls, respectively comply with National Cholesterol Education

Programme recommendation (National Heart Lung and Blood Institute, 1988). Anticoagulated blood was gently mixed with blood mixer (Sarstedt, D-5223, Numbrecht, West Germany). Haemoglobin concentration was estimated with Sysmex (KX-21N) and Cluster of differentiation 4 (CD_4) was done with Becton Dickinson FACSCount® (BD Biosciences, San Jose, CA 95131 USA). The fluoridated anticoagulated blood was centrifuged (Zentrifugen, D-78532, Tuttlingen, Germany) at 3000 rpm for 5 min to separate the plasma from the deposit. The plasma was used to estimate the fasting blood glucose.

Systolic and diastolic blood pressures were measured with a mercury sphygmomanometer (Dekamet MK.3, England). Two readings were made after the subject was made to rest for about five minutes and the mean readings recorded.

Data analysis and statistics: Results were expressed as Means±SEM. Data were analysed by one-way ANOVA followed by the Bonferroni test for multiple comparison using Graph Pad Prism version 4 (Graph Pad Software, San Diego California). Unpaired Student t-tests were used to assess for significance. Statistical significance was set at p-values = 0.05 for the various parameters in the study. A linear regression and multivariate regression analyses, was done to find predictors of cardiovascular risk from the various parameters.

RESULTS

Table 1 presents the biochemical and haematological indicators of the study population. The means of CD4, haemoglobin (Hb), Fasting Blood Sugar (FBS) total cholesterol, High density lipoprotein and low density lipoprotein for HAART-experienced groups were statistically significantly higher ($p<0.001$) than the HAART-naive group. There was no significant change in the triglyceride levels ($p = 0.9967$). The biochemical presentation is similar between males and females. The liver function test enzymes, Aspartate amino Transferase (AST) and Alanine amino Transferase (ALT) were significantly ($p<0.0009$) reduced in the HAART experienced but with no significant change in the CKMB levels. A similar trend was observed between the sexes and the control.

The effects of HAART on blood pressure was also studied (Table 2). Twenty five patients, representing 15.2% (25/164) of HAART-experienced participants (164) developed systolic

Table 1: Biochemical variables of the study population

Variables	Control (N = 1)	Case (N = 164)	Control female (N = 86)	Female cases (N = 122)	Control male (N = 55)	Male cases (N = 42)
Hb (g dL^{-1})	10.43±0.14	11.77±0.12***	10.44±0.17	11.69±0.14***	10.42±0.26	12.01±0.22***
CD4 (cells uL^{-1})	233.35±16.69	358.71±17.29***	258.36±23.85	370.85±20.89***	194.24±20.15	323.45±29.29***
FBS (mmol L^{-1})	3.81±0.08	4.48±0.17***	3.81±0.11	4.59±0.21**	3.81±0.13	4.16±0.24
TC (mmol L^{-1})	3.65±0.08	4.54±0.08***	3.80±0.10	4.69±0.09***	3.43±0.13	4.09±0.15**
TRIG (mmol L^{-1})	1.37±0.07	1.37±0.07	1.35±0.09	1.38±0.08	1.40±0.11	1.34±0.13
HDLC (mmol L^{-1})	0.85±0.04	0.97±0.03*	0.92±0.05	1.01±0.04	0.73±0.06	0.86±0.06
LDLC (mmol L^{-1})	2.24±0.07	2.87±0.07***	2.29±0.08	2.98±0.09***	2.16±0.10	2.53±0.09
AST (U L^{-1})	34.74±1.80	27.38±1.26***	33.39±2.31	27.56±1.61*	36.86±2.90	26.87±1.49*
ALT (U L^{-1})	27.78±1.62	22.06±1.06**	23.64±1.68	21.29±1.35	34.24±3.05	24.28±1.26*
CKMB (U L^{-1})	25.67±1.42	25.88±1.44	27.41±1.56	26.07±1.72	22.95±2.68	25.30±2.63

Hb: Haemoglobin concentration, FBS: Fasting blood glucose, TC: Total cholesterol, TRIG: Triglycerides, HDLC: High density lipoprotein cholesterol, LDLC: Low density lipoprotein cholesterol, CD4: Clnster of differentiation 4, AST: Aspartate amino Transferase, ALT: Alanine amino Transferase and CKMB: Creatine Kinase-MB and S.E: Standard error of the mean, *p<0.05, **p<0.01, ***p<0.001

Table 2: Effect of duration of therapy on blood pressure

	Systolic hypertension frequency			Diastolic hypertension frequency		
Duration of therapy	Total	Male	Female	Total	Male	Female
6-18	13	6	7	21	6	15
19-31	7	2	5	11	2	9
31+	5	1	4	7	2	5
Total	25	9	16	39	10	29

hypertension, at least 6 months on therapy. Conversely, thirty-nine patients, representing 23.8% (39/164) of the HAART-experienced, developed diastolic hypertension. However, the number of patients with hypertension rather seemed to reduce with duration of therapy. Thirteen patients (7.9%) of HAART-experienced developed systolic hypertension between 6-18 months, seven patients (4.3%) developed systolic hypertension between 19-31 months and five patients (3.0%) after, 31 months on therapy. The trend was similar in diastolic blood pressure. Twenty one patients representing 12.8% (21/164) of HAART-experienced participants developed diastolic hypertension between 6-18 months on therapy. Eleven patients (6.7%) developed diastolic hypertension between 19-31 months whilst, seven (4.3%) HAART-experienced participants developed diastolic hypertension after 31 months.

The results in Table 3, show that high plasma concentrations of glucose, was positively ($p = 0.0068$) associated with cardiovascular risk. Aspartate amino transferase, Alanine amino transferase and Creatine Kinase-MB were also positive $p<0.0047$) associated with cardiovascular risk as well as low concentration HDL ($p = 0.0012$).

Table 4 depicts the analysis of the effect of different HAART regimen on morbidity conditions and the development of hypertension. Comparing morbidity conditions and the type of HAART regimen used revealed that, 7.1% of the participants who developed systolic hypertension used d4T/3TC/NVP combination therapy, while 2.6, 1.9 and 1.9% systolic hypertensive HAART-experienced participants used d4T/3TC/EFV, AZT/3TC/NVP and AZT/3TC/EFV, respectively (Table 4).

The risk of developing systolic and diastolic hypertension for HAART-experienced group was about 5 times compared to the HAART- naive group, (data not shown). Also 11.6% (18/164) diastolic hypertensive HAART-experienced participants used d4T/3TC/NVP and 3.9% (6/164), 5.2% (8/164) and 1.9% (3/164) diastolic hypertensive patients used d4T/3TC/EFV, AZT/3TC/NVP and AZT/3TC/EFV, respectively (Table 4).

Systolic and Diastolic blood pressures, markers of CAD were significantly ($p<0.05$) positively correlated to duration of HAART and total cholesterol, but positively and significantly correlated to Hb, whilst systolic blood pressure was negatively non significantly correlated to CD4 count. Haemoglobin is positively and significantly ($p<0.001$) correlated to systolic and diastolic pressures (Table 5).

DISCUSSION

Infection with human immunodeficiency virus (HIV) and treatment with antiretroviral drugs may affect the function of the heart and its structures. Endothelial dysfunction is, followed by the clinical manifestations of atherosclerosis (Celermajer, 1997). The mechanism of HIV-related endothelial dysfunction is not clear but may involve lipid disorders associated with HIV infection (Grinspoon and Carr, 2005). Clinical studies among HIV-1-infected patients on HAART

Table 3: Biochemical risk factors associated with cardiovascular disease

Parameters	Control	Case	OR (95% CI)	Chi^2	p-value
FBS (mmol L^{-1})					
Low	83(58.9)	86(52.4)	0.9(0.6-1.5)	0.08	0.7780
*Normal	55(39.0)	61(37.2)	1		
High	3(2.1)	17(10.4)	5.1(1.3-28.4)	7.33	0.0068
TC (mmol L^{-1})					
Low	45(31.9)	15(9.2)	0.2(0.1-0.4)	23.68	0.0000
*Normal	95(76.4)	143(87.2)	1		
High	1(0.7)	6(3.7)	4.0(0.5-185.2)	1.87	0.1710
TRIG (mmol L^{-1})					
Low	0(0)	1(0.6)	------	0.87	0.3502
*Normal	113(80.1)	129(78.7)	1		
High	28(19.9)	34(20.7)	1.1(0.6-1.9)	0.05	0.8290
HDLC (mmol L^{-1})					
Low	84(59.6)	71(43.3)	0.4(0.3-0.8)	10.44	0.0012
*Normal	48(34.0)	88(53.7)	1		
High	9(6.4)	5(3.1)	0.3(0.1-1.1)	4.53	0.0333
LDLC (mmol L^{-1})					
Low	138(97.9)	143(87.2)	0.1(0.0-0.6)	8.98	0.0027
*Normal	2(1.4)	15(9.2)	1		
High	1(0.7)	6(3.7)	0.8(0.0-55.0)	0.03	0.8652
CD_4 (cells uL^{-1})					
*Low	52(36.9)	18(11.0)	1		
Normal	89(63.1)	146(89.0)	4.7(2.5-9.1)	28.77	0.0000
AST (U L^{-1})					
*Normal	104(73.8)	142(86.6)	1		
High	37(26.2)	22(13.4)	0.4(0.2-0.8)	7.99	0.0047
ALT (U L^{-1})					
*Normal	114(80.9)	152(92.7)	1		
High	27(19.2)	12(7.3)	0.3(0.1-0.7)	9.52	0.0020
CKMB (U L^{-1})					
*Normal	72(51.1)	96(58.5)	1		
High	69(48.9)	41(46)	0.4(0.3-0.7)	10.50	0.0012

FBS: Fasting blood glucose, TC: Total cholesterol, TRIG: Triglycerides, HDLC: High density lipoprotein cholesterol, LDLC: Low density lipoprotein cholesterol, CD_4: Cluster of differentiation 4, AST: Aspartate Amino Transferase, ALT: Alanine Amino Transferase, CKMB: Creatine Kinase-MB

demonstrate increased levels of apoB and apoC-III and decreased levels of apoE lipoproteins (Lenhard *et al*., 2000 Bonnet *et al*., 2001; Mooser and Carr, 2001; Fauvel *et al*., 2001). Such an atherogenic profile is likely to increase the risk of cardiovascular complications including myocardial infarction and premature atherosclerosis (Mehta and Reilly, 2005; Carr, 2003).

The surrogate markers of atherosclerosis; total cholesterol and LDL were significantly ($p<0.001$) elevated in the HAART experienced subjects than the HAART-naïve (Table 1). Prolonged elevated levels of LDL and total cholesterol increase the development of atherosclerosis (Ross and Harker, 1976; Martin *et al*., 1999). Premature and or accelerated development of atherosclerosis in antiretroviral treated HIV-infected individuals has been reported (Fichtenbaum, 2003). The blockade of the blood vessel lumen increases blood pressure which if uncontrolled results in cardiovascular diseases. Even though the plasma levels of TC and LDL in both the

Table 4: Morbidity conditions and the type of HAART regimen

		HAART regimen				
Morbidity conditions	Case n = 164 (%)	d4T/3TC/NVP (n = 68)	d4T/3TC/EFV (n = 30)	AZT/3TC/NVP (n = 36)	AZT/3TC/EFV (n = 21)	Control (n = 141)
Hb(g dL^{-1})						
Anaemia	27(16.5)	14(9.0)	8(5.2)	1(0.6)	1(0.6)	65(46.1)
Normal	131(79.9)	53(34.2)	20(12.9)	33(21.3)	20(12.9)	76(53.9)
High	6(3.7)	1(0.6)	2(1.3)	2(1.3)	0(0.0)	0(0.0)
FBS (mmol L^{-1})						
Normal	153(93.3)	63(40.6)	27(17.4)	36(23.2)	19(12.3)	139(98.6)
Diabetes	11(6.7)	5(3.2)	3(1.9)	0(0.0)	2(1.3)	2(1.4)
TC (mmol L^{-1})						
Low	15(9.1)	8(5.2)	2(1.3)	3(1.9)	2(1.3)	45(31.9)
Normal	143(87.2)	60(38.7)	27(17.4)	32(20.6)	17(11.0)	95(67.4)
High	6(3.7)	0(0.0)	1(0.6)	1(0.6)	2(1.3)	1(0.7)
TRIG (mmol L^{-1})						
Low	1(0.6)	0(0.0)	0(0.0)	1(0.6)	0(0.0)	0(0.0)
Normal	129(78.7)	54(34.8)	19(12.3)	29(18.7)	19(12.3)	113(80.1)
High	34(20.7)	14(9.0)	11(7.1)	6(3.9)	2(1.3)	28(19.9)
HDLC (mmol L^{-1})						
Low	71(43.3)	28(18.1)	16(10.3)	12(7.7)	9(5.8)	84(59.6)
Normal	88(53.7)	38(24.5)	13(8.4)	22(14.2)	12(7.7)	48(34.0)
High	5(3.0)	2(1.3)	1(0.6)	2(1.3)	0(0.0)	9(6.4)
LDLC (mmol L^{-1})						
Low	143(87.2)	63(40.6)	28(18.1)	33(21.3)	17(11.0)	138(97.9)
Normal	15(9.1)	4(2.6)	1(0.6)	2(1.3)	2(1.3)	2(1.4)
High	6(3.7)	1(0.6)	1(0.6)	1(0.6)	2(1.3)	1(0.7)
AST (U L^{-1})						
Normal	142(86.6)	59(38.1)	25(16.1)	30(19.4)	20(12.9)	104(73.8)
High	22(13.4)	9(5.8)	5(3.2)	6(3.9)	1(0.6)	37(26.2)
ALT (U L^{-1})						
Normal	152(92.7)	64(41.3)	26(16.8)	33(21.3)	21(13.5)	114(80.9)
High	12(7.3)	4(2.6)	4(2.6)	3(1.9)	0(0.0)	27(19.1)
CKMB (U L^{-1})						
Normal	96(58.5)	36(23.2)	21(13.5)	23(14.8)	11(7.9)	72(51.1)
High	68(41.5)	32(20.6)	9(5.8)	13(8.4)	10(6.5)	69(48.9)
SBP (mm Hg^{-1})						
Normal	139(84.8)	57(36.8)	26(16.8)	33(21.3)	18(11.6)	136(96.5)
SH	25(15.2)	11(7.1)	4(2.6)	3(1.9)	3(1.9)	5(3.5)
DBP (mm Hg^{-1})						
Normal	125(76.2)	50(32.3)	24(15.5)	28(18.1)	18(11.6)	132(93.6)
DH	39(23.8)	18(11.6)	6(3.9)	8(5.2)	3(1.9)	9(6.4)

Hb: Blood haemoglobin, FBS: Fasting blood glucose, TC: Total cholesterol, TRIG: Triglycerides, HDLC: High density lipoprotein cholesterol, LDLC: Low density lipoprotein cholesterol, AST: Aspartate Amino Transferase, ALT: Alanine Amino Transferase, CKMB: Creatine Kinase-MB, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

HAART-experienced and HAART-naïve were within the physiological levels (Table 1), but the fact that the levels in the HAART-experience were statistically significantly higher, implies an increased tendency to the development of CVD. Several studies have implicated HAART, to increased level

Table 5: Pairwise correlation coefficients of clinical, biochemical and anthropometric indices of the study population: case (on the lower left-hand side) and control (on the upper right-hand side)

	Hb	CD_4	DT	FBS	TC	SBP	DBP
Hb		0.20*	--	-0.07	0.14	0.30***	0.43***
CD_4	0.24**		--	-0.05	-0.02	0.14	0.25**
DT	0.31***	0.20*		--	--	--	--
FBS	0.02	0.08	0.04		0.02	-0.01	-0.01
TC	0.18*	0.03	0.16*	0.21**		0.18*	0.15*
SBP	0.27***	-0.02	0.15*	0.07	0.23**		0.68***
DBP	0.20*	0.01	0.13*	0.09	0.09	0.81***	

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed), ***Correlation is significant at the 0.001 level (2-tailed), HB: Haemoglobin, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, DT: Duration of therapy, FBS: Fasting blood glucose, TC: Total cholesterol

of plasma, TC and LDL and decreased HDL and increased central fat accumulation (Carr *et al.*, 1999). There was no significant change in the plasma levels of triglycerides. This is probably because many of the subjects were engaged in some amount of exercise as part of the treatment regimen. Triglycerides are used as source of energy, even mild to moderate exercise can lower plasma triglycerides levels (Decombaz *et al.*, 1983). A similar trend in plasma lipid levels was observed between the sexes. This support the fact that deranged lipid profile was due to HAART and not gender related. It is also possible that this observation could be explained by the low fat dietary differences in the Ghanaian as compared to the fat rich western diet, or due to the dietary restriction as part of treatment package. Indeed, HIV-infected patients require vigorous treatment including low-fat diets, avoidance of simple sugars and elimination of alcohol intake (Green, 2002).

The suspicion that the use of HAART could result in the development of CVD, a fact that is disputed by some researchers on the basis that atherogenic effect of hyperlipidaemia could take over 10-15 years to develop (Martin *et al.*, 1999) and the short time use of HAART between 2-3 year cannot exclusively be attributed to be the sole cause of CVD.

In this study, the development of systolic and diastolic hypertension depends on the duration of HAART (Table 2). The rates of cardiovascular events among persons with HIV infection increased with the duration of exposure to HAART containing protease inhibitors (Currier *et al.*, 2003; Friis-Moller *et al.*, 2007). Within six months, 15.2% of HAART-experienced participants developed systolic hypertension. While 23.8% developed diastolic hypertension and within 6-18 months 7.9% developed systolic hypertension while 12.8% developed diastolic hypertension.

However, the number of patients with hypertension rather seemed to reduce with duration of therapy. This may probably be due to early death, consistent with the decrease in the number of HIV patients with the duration of the disease. The rate of death of HIV-infected patients in Africa, the highest in the world is due to lack of antiretroviral drugs, poor nutrition and poor counseling/management (Weiser *et al.*, 2009; Morgan *et al.*, 2002).

Several studies have shown that highly active anti-retroviral drugs have hepatotoxic effect (Qurishi *et al.*, 2003; Rodriguez-Rosado *et al.*, 1998), hence the delay in the introduction of HAART until the CD_4 count falls below 350 to minimize the toxic effect of these drugs. Most antiretroviral medications have been associated with liver enzyme elevation, an indication of hepatotoxicity, although certain drug combinations may cause less liver damage or non (Palmon *et al.*, 2002). Several mechanisms of hepatotoxicity have been postulated, including metabolic host-medicine injury, hypersensitivity reactions, mitochondrial toxicity and immune reconstitution phenomena

(Soriano *et al.*, 2008). Surprisingly, the combination of drugs in the HAART-experienced was rather hepato-protective according to this study. The enzymes assayed for as liver function test, serum aspartate aminotransferase (AST) and serum alanine aminotransferase) (ALT) were significantly ($p<0.001$) reduced in the HAART-experienced subjects, an indication of liver protection rather than cytotoxic effect. AST and ALT are mitochodrial and membrane bound hepatocellular enzymes respectively and are released into plasma when there is hepatocellular damage and the plasma levels are usually raised. However, HIV infection results in an increase in endogenous interferon alpha production and that may suppress the transaminases levels, but following anti-retroviral therapy interferon levels then return to normal (Rutschmann *et al.*, 1998). It is also possible that these drugs have a two phase action, first protective, but the cumulative effect is cytotoxic, hence the period of study in this work may be too short to reveal the cytotoxic effect, but at least the drugs seems to show some cytotoxic protective effect in the early stages of treatment. Hepatotoxic effect of HAART is time dependent (Powderly, 2002). This effect may also depend on the HAART combination.

The effects of the biochemical risk factors of cardiovascular diseases are expressed in Table 3. High plasma glucose concentration significantly ($p = 0.0068$) increase a cardiovascular risk. This is particularly the case in uncontrolled diabetes, leading to a metabolic syndrome (Sattar *et al.*, 2003) and therefore a cardiovascular risk. Also high LDL concentration and the significantly low HDL ($p = 0.0012$) are associated with metabolic syndrome and these are cofactors of cardiovascular risk. A significantly increased plasma concentration of Aspartate amino transferase, Alanine amino transferase and Creatine Kinase-MB ($p<0.0047$) is associated with a cardiovascular risk. High plasma level of liver enzymes is an indication of hepatocellular toxicity and the degree of viral load. This work has shown that an increased in cardiovascular risk is associated with the duration of HAART (Table 4).

Apart from duration of HAART on the development of hypertension, the morbidity conditions and the type of HAART regimen used revealed that, the combination and or individual drugs have a morbidity risk. Indeed 7.1% participants who developed systolic hypertension used d4T/3TC/NVP combination therapy, while 2.6, 1.9 and 1.9% systolic hypertensive HAART experienced participants used d4T/3TC/EFV, AZT/3TC/NVP and AZT/3TC/EFV, respectively (Table 4).

Systolic and Diastolic blood pressures, markers of CAD were significantly ($p<0.05$) positively correlated to duration of HAART and total cholesterol (Table 5). The association between these parameter and CAD has been proven by several studies (Holmberg *et al.*, 2002; Friis-Moller *et al.*, 2003). Even though cardiovascular disease among HIV-infected persons are not currently high enough it is still advisable to take appropriate measures to reduce CAD risks.

CONCLUSION

The increase in plasma levels of LDL and Total cholesterol is a poor prognosis to the development of CVD. Diastolic pressure and systolic blood pressure were significantly elevated within six months of HAART. Diastolic pressure, systolic pressure and total cholesterol key markers for the development of cardiovascular diseases were positively correlated to duration of HAART. Some combinations of highly active antiretroviral drugs were cardio protective in the short run.

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