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Burden of subclinical carotid atherosclerosis and vascular risk factors among people living with HIV in Ghana

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ABSTRACT

Background: The burden of cardiovascular disease (CVD) among people living with HIV (PLWH) in sub-Saharan Africa is projected to rise due to a rapid epidemiological transition and improved treatment of HIV infection on the sub-continent.

Objective: The Evaluation of Vascular Event Risk while on Long-term Anti-retroviral Suppressive Therapy (EVERLAST) Study sought to assess the extent of subclinical atherosclerosis and characterize the nature of CVD risk factors among HIV patients on Antiretroviral therapy (ART) in Ghana.

Methods: We conducted a cross-sectional study involving HIV patients on antiretroviral therapy (n = 250) in comparison with HIV positive ART naïve (n = 201), and HIV uninfected controls (n = 250). We assessed prevalence of hypertension, dyslipidemia, diabetes mellitus, central obesity, and carotid atherosclerosis using B-mode carotid Doppler ultrasonography. We assessed factors associated with subclinical atherosclerosis defined by a carotid intimal media thickness (CIMT) cut-off of ≥0.78 mm among PLWH using a logistic regression model.

Results: Mean age of PLWH on combination ART (cART) was 45.7 ± 8.6 years, 42.9 ± 8.8 years among PLWH not on cART, and 44.9 ± 9.5 years among HIV negative controls of which 81.2%, 81.6% and 81.1% respectively were females. Prevalence of subclinical atherosclerosis at the common carotid artery in the three groups was 67.6%, 66.7% and 62.4%, p = 0.43. Among PLWH, raised serum total cholesterol (OR 1.16, 95% CI: 1.00–1.35) and triglycerides (OR 1.32, 95% CI: 1.01–1.73) were significantly associated with subclinical atherosclerosis. Prevalence of vascular risk factors among PLWH on cART, PLWH cART naïve, and HIV negative controls respectively were as follows: dyslipidemia- 79.5%, 83.1%, and 73.5%, p = 0.04; hypertension- 40.2%, 23.4%, and 44.9%, p < 0.0001; central obesity-61.8%, 66.7%, and 78.2%, p < 0.0001; diabetes mellitus-6.8%, 5.5% and 4.9%, p = 0.53.

Conclusion: Overall while there is a high baseline prevalence of CVD risk factors in the Ghanaian population, serum lipid derangements appear to be more prevalent among HIV infected patients, and are linked to subclinical atherosclerosis. Future studies need to confirm these findings, explore the underlying pathophysiology, and optimize treatment strategies to avert untoward CVD outcomes.

1. Introduction

The introduction of and accelerated global access to potent, combination antiretroviral therapy (cART) has resulted in significant declines in mortality and morbidity due to HIV infection [1,2]. In 2016, 17 million of the 37 million people living with HIV (PLWH) worldwide were receiving cART, resulting in a 43% decline in AIDS-related deaths [3]. However, while the massive rollout of cART has led to a decline in deaths from AIDS related opportunistic infections and malignancies, there has correspondingly been a surge in deaths from cardiovascular

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disease (CVD) [4–10]. The heightened CVD risk in HIV is due to a combination of factors including the persistent immune activation and inflammation from HIV infection [11,12], pro-atherogenic lipid abnormalities induced by HIV infection and cART treatment [13,14], and traditional risk factors such as hypertension, diabetes mellitus and metabolic syndrome, and lifestyle factors such as cigarette smoking, alcohol use, and eating patterns [15].

Sub-Saharan Africa has experienced an exponential rise in the proportions of PLWH receiving cART administered widely in programmatic settings. This paradigm shift has been driven largely by recent guidelines recommending cART use in all HIV-infected individuals, regardless of CD4+ T-cell counts [16]. With PLWH living longer on cART, new infections treated earlier and a growing burden of cardiovascular risk factors such as hypertension, dyslipidemia, and obesity due to adoption of western lifestyles in SSA, CVD risk among PLWH is expected to rise. Given the significant morbidity and mortality associated with overt CVD in SSA, early detection and prompt management of CVD risk factors and subclinical predictors of CVD risk is an urgent priority in the continent.

Evaluation of the carotid artery intima-media thickness (CIMT) for evidence of subclinical atherosclerosis has been investigated in cross-sectional and prospective studies as a marker of CVD risk in the HIV population [17–20]. The key determinants of subclinical carotid atherosclerosis and its progression from studies conducted in high income countries (HIC) include use of protease inhibitors, cardio-metabolic and lifestyle factors such as cigarette smoking, and HIV-related factors such as nadir CD4 counts and inflammation [17–20]. However in SSA, a large proportion of PLWH are females and non-cigarette smokers who are treated using non-nucleoside reverse transcriptase inhibitors as preferred first-line [21] instead of protease inhibitors according to WHO recommendations. The implication is that the risk factors for subclinical atherosclerosis in resource-limited settings may differ from those observed for cohorts in HICs. Two previous studies from SSA found that up to 24% of Ugandan HIV patients receiving cART, versus 14% of those who were ART naïve, had evidence of asymptomatic systemic atherosclerosis based on sonographic measurements of carotid intimal media thickness (CIMT) [22]. Furthermore, CIMT values among a predominantly female South African HIV+ population were considerably elevated and were associated with established CVD risk factors such as hypertension, high Body Mass Index (BMI), diabetes mellitus, total and low-density lipoprotein cholesterol, estimated GFR, metabolic syndrome, and Framingham Heart Risk score rather than HIV-related factors [23]. In both of these studies, non-HIV infected controls were not evaluated, thereby limiting the validity of relative risk calculations of CVD observed. The Evaluation of Vascular Event Risk while on Long-term Anti-retroviral Suppressive Therapy (EVERLAST) Study sought to assess the burden of subclinical atherosclerosis using carotid intimal media thickness (CIMT) and characterize the burden of CVD risk factors among HIV patients on ART in Ghana compared with PLWH who are cART naïve and HIV negative controls.

2. Methods

2.1. Study design & population

The Evaluation of Vascular Event Risk while on Long-term Anti-retroviral Suppressive Therapy (EVERLAST) Study is designed as a case-control study to compare CVD risk by measuring the CIMT and the presence of traditional vascular risk factors among Ghanaian PLWH on cART compared with age- and sex-matched HIV uninfected controls as well as PLWH who cART naive. Ethical approval for the study was obtained from the Kwame Nkrumah University of Science and Technology Committee of Human Research Publications and Ethics. Cases were PLWH aged ≥30 years receiving cART for at least 1 year at the HIV clinic of the Komfo Anokye Teaching Hospital, a tertiary medical facility in Kumasi, Ghana. Kumasi is the second largest metropolitan city in Ghana with an estimated population of 2 million. We consecutively enrolled 201 PLWH aged ≥30 years who were cART naïve at the HIV clinic matched by sex and age band of ± 5 years. We also enrolled 250 age- and sex-matched community dwelling controls who were confirmed HIV negative after serological testing.

Controls were enrolled from communities in and around suburbs of the metropolitan city of Kumasi. At each community, we contacted a community leader to inform them about the purpose of our study and for community entrance to conduct the study. On an agreed date, an announcement is made for those interested in the study to come to a Community center for potential enrollment of consecutive adults into the study if inclusion and exclusion criteria were met. The study questionnaires were completed by Research Assistants upon interviewing study participants; vital signs and anthropometric indicators were collected by research nurses, fasting blood samples were collected by phlebotomists and sent to the Research laboratory for processing within 4 h. To meet inclusion criteria as HIV sero-negative, control subjects were tested for HIV. Community controls were matched as closely as possible for age and sex to our HIV cohort. Controls were thus not enrolled from healthcare clinic settings.

2.2. Study evaluations

A standardized data collection form was developed to collect information on socio-demographic characteristics, including age, sex, educational status, income, and marital status. Among the PLWH, we collected data via interview and through medical record chart extraction on HIV disease characteristics, such as current CD4 cell count, HIV-1 viral load, past and current history of cART, duration on cART. We assessed the traditional vascular risk factors using history taking, physical examination, and by collecting blood samples for HBA_{1c} and fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides). The following definitions were used for traditional vascular risk factors.

- Blood pressure (BP) (mean of three measurements) was taken on each study participant following a standard protocol. A cut-off of at least 140/90 mmHg, a history of hypertension, or use of anti-hypertensive drugs were each regarded as indicators of hypertension.
- Diabetes was defined as a history of known diabetes, use of diabetes medications, or an HBA_{1c} > 6.5%. Pre-diabetes was defined as having an HBA1c of 5.7–6.4% [24].
- Dyslipidemia was defined as a fasting total cholesterol concentration of at least 5.2 mmol/l, HDL cholesterol 1.03 mmol/l or lower, LDL cholesterol at least 3.4 mmol/l, or serum triglyceride of at least 1.7 mmol/l, according to National Cholesterol Education Program guidelines [25].
- Obesity was defined using the WHO guidelines with a Waist-to-Hip ratio (WHR) cut-off of 0.90 (men) and 0.85 (women) or body mass index (BMI) of 30 kg/m^2 for obesity [26].
- Physical activity was defined as regular involvement in moderate exercise (walking, cycling, or gardening) or strenuous exercise (jogging, football, and vigorous swimming) for 4 h or more per week and was assessed via self-report.
- Dietary history included frequency of intake of green leafy vegetables, fruits, and addition of salt at the table.
- Alcohol users were categorized into three groups (never consumed, or current users). Similarly, smoking status was also categorized into three groups (those who have never smoked, former smokers, and individuals who smoked any tobacco in the past 12 months).

2.3. Main outcome measure

The primary endpoint was carotid artery intima-media thickness (CIMT). It is an intermediate phenotype for early atherosclerosis and

can be measured relatively simply and non-invasively on B-mode ultrasound. Carotid Intima-media thickness (CIMT) was measured at 1 cm portions of the distal left and right common carotid artery far and near walls with a linear transducer (transducer frequency of 7.5 MHz) with axial resolution of 0.10 mm, and calculated automatically over 3 cardiac cycles following the Mannheim consensus [27]. The average thickness of the left and right common carotid arteries (CCA) obtained at 3 angles (anterior, lateral and posterior bilaterally) at the optimum angle of insonation was reported as the overall CIMT for the CCA [28]. Measurements were also taken at the carotid bifurcations and internal carotid arteries (ICA) bilaterally. Presence of plaques defined as an area of with localized IMT > 1.5mm [27] were also noted. Replicate image acquisitions were independently performed by two trained sonographers who were blinded to the status of study participants and risk factor status. Subclinical atherosclerosis was defined using a cut-off value of CIMT of ≥0.78 mm, based on an observation that on average a healthy adult reaches a CIMT of 0.78 mm at the age of 76 [29]. We also assessed factors associated with a CIMT cut-off of ≥1.0 mm, which is the highest CIMT cut-off used in a previous study [30].

2.4. Statistical analysis

Comparisons of demographic, lifestyle, vascular risk factors, and CIMT among the three groups (PLWH on cART, PLWH not on cART, and HIV negative controls) were performed using analysis of variance for continuous parametric variables and chi-square tests for discrete variables. Pairwise comparisons between the three groups were also performed using Student's *t*-test and Chi-squared tests. Sub-clinical atherosclerosis was defined as a CIMT ≥ 0.78 mm as a primary outcome measure and predictors of this outcome in the entire PLWH cohort, PLWH on cART, and PLWH not on cART were assessed using bivariate and multivariate logistic regression. Since we did not perform a 1:1 matching of cases with controls with regards to age and sex, an unconditional logistic regression model approach was adopted. Putative factors included in models were demographic variables such as age, sex, location of residence, anthropometric measures, such as WHR, traditional vascular risk factors such as hypertension, diabetes, lipid subfractions (i.e. total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides), dietary factors (vegetable and fruit intake); HIV-related factors such as WHO clinical stage, CD4 counts, viral load after log transformation, or a dichotomous variable < 50 copies/ml or higher. Factors with a *p*-value of < 0.05 were included in a multivariable model. In secondary analysis, factors associated with a higher CIMT cut-off ≥1.0mm [30] were also assessed using the same set of putative variables. In all analyses, a p-value of < 0.05 was considered statistically significant. Statistical analysis was performed using GraphPad Prism version 7 and SPSS version 21.

3. Results

3.1. Demographic characteristics of study participants

We enrolled 250 HIV patients receiving cART (PLWH on cART), 201 HIV patients not receiving cART (PLWH cART naïve), and 250 HIV sero-negative individuals (HIV negative controls). There were 203 (81.2%) females among the PLWH on cART, 164 (81.6%) females among the PLWH cART naïve group, and 202 (81.1%) females among the HIV negative controls, p = 0.99. Mean age among PLWH on cART was 45.7 ± 8.6 years comparable with 44.9 ± 9.5 years among HIV negative controls but higher than 42.9 ± 8.8 years among PLWH cART naïve, p = 0.003. Many more of the PLWH cART naïve group resided in urban residence (76.9%), compared with PLWH on cART (67.6%) and HIV negative controls (66.8%), p = 0.04 (by ANOVA). The three groups differed significantly in other demographic characteristics such as educational status, marital status, employment, and monthly income levels, as shown in Table 1.

3.2. HIV Specific clinical characteristics

Among the PLWH on cART, mean ± SD duration of HIV diagnosis was 8.6 ± 4.4 years, with duration on cART being 7.7 ± 3.6 years. First-line cART (n = 241) comprised of a backbone of dual nucleoside reverse transcriptase inhibitor (NRTI) of zidovudine plus lamivudine 136 (56.4%), tenofovir plus lamivudine/emtracitabine 58 (24.1%), or stavudine plus lamivudine 47 (19.5%) with non-nucleoside reverse transcriptase inhibitor (NNRTI) of either efavirenz 140 (58.1%) or nevirapine 101 (41.9%). Only 4 patients were on second line therapy with ritonavir-boosted lopinavir. There were 152 out of 250 (60.8%) PLWH on cART with suppressed viremia, below 20 copies/ml and with a mean CD4 T-cell count of 641.9 ± 331.5 cells/cm^3. The laboratory and clinical characteristics of the PLWH cART naïve group are shown in Table 1.

3.3. Burden of cardiovascular and lifestyle risk factors

The prevalence of hypertension was highest among the HIV negative control group (44.9%) followed by PLWH on cART at 36.9%, and the PLWH cART naïve with 23.4%, p < 0.0001. Among those with hypertension, 44.7% of PLWH cART naïve, 40.2% of PLWH on cART, and 29.7% HIV negative controls were on antihypertensive therapy with corresponding BP control rates of 42.9%, 29.7%, and 45.5% respectively. The prevalence of dyslipidemia was highest among PLWH cART naïve (83.1%), followed by PLWH on cART at 79.5%, and lastly HIV negative controls with 73.5%, p = 0.04. There were differences in the lipid sub-fraction perturbations in the three groups as shown in Table 2. For instance, while the PLWH cART naïve group had the highest concentrations of serum total cholesterol, LDL-cholesterol, and triglycerides, the PLWH on cART had the highest proportion with low HDL-cholesterol among the 3 groups. Notably, none of the study participants in the three groups were receiving lipid-modifying therapy. Diabetes mellitus prevalence declined from 6.8% among PLWH on cART, to 5.5% in PLWH cART naïve, and 4.9% among HIV negative controls, with similar trend in pre-diabetes rates of 25.7%, 23.9%, and 20.5% respectively, p = 0.53. Obesity, assessed using a BMI > 30 kg/m^2 was highest among HIV negative control at 34.8%, 27.1% among PLWH on cART, and 16.4% among PLWH cART naïve, p < 0.0001 with a similar trend in waist-to-hip ratio as depicted in Table 2. Overall, prevalence of metabolic syndrome was comparable among the three groups being 39.7% among HIV negative controls, 38.2% in the PLWH on cART, and 32.3% among PLWH cART naïve, p = 0.25.

Generally, cigarette use was low among the three groups; however, rates of current alcohol use was higher among PLWH being 8.5% in cART naïve and 8.0% in those on cART versus 3.2% among HIV negative controls, p = 0.03. Regular physical activity rates were highest among PLWH on cART group (38.0%) and least among PLWH cART naïve (22.4%), p = 0.001; conversely, vegetable consumption of > 2 servings daily was highest among PLWH cART naïve (38.1%) and lowest among PLWH on cART (19.0%), p < 0.0001. (Table 1).

3.4. Sub-clinical carotid atherosclerosis

There were no discernible differences in the mean ± SD common carotid intimal media thickness between the three groups being 0.869 ± 0.174 mm among PLWH cART naïve, 0.867 ± 0.198 mm among PLWH on cART, and 0.856 ± 0.189 mm among HIV negative controls, p = 0.73. Applying a CIMT cut-off of ≥0.78 mm as definition for sub-clinical carotid atherosclerosis yielded prevalence rates of 169/250 (67.6%) among PLWH on cART, 134/201 (66.7%) among PLWH cART naïve, and 156/250 (62.4%) among the HIV negative group, p = 0.43. Among the entire HIV cohort, factors associated with CIMT of ≥0.78 mm in unadjusted analysis were raised total cholesterol, OR of 1.16 (1.00–1.35), and raised serum triglyceride, OR of 1.32 (1.01–1.73), p = 0.044. (Table 3). However, none of these factors were

Table 1
Baseline demographic & lifestyle characteristics of EVERLAST study participants.

Characteristic	HIV on cART (Group A) n = 250	HIV not on cART (Group B) n = 201	HIV negative controls (Group C) n = 250	P-value (A vs B vs C)	P-value (A versus B)	P-value (A versus C)	P-value (B versus C)
Female, n (%)	203 (81.2)	164 (81.6)	202 (81.1)	0.99	0.99	0.99	0.99
Age, mean ± SD	45.7 ± 8.6	42.9 ± 8.8	44.9 ± 9.5	0.003	0.0006	0.28	0.02
Location of residence				0.04	0.03	0.85	0.02
Urban	169 (67.6)	153 (76.9)	167 (66.8)				
Rural	81 (32.4)	46 (23.1)	83 (33.2)				
Educational Status				0.03	0.06	0.01	0.74
No formal education	69 (27.6)	54 (27.1)	76 (30.5)				
Primary	100 (40.0)	58 (29.2)	67 (26.9)				
Secondary	67 (26.8)	72 (36.2)	83 (33.3)				
Tertiary	14 (5.6)	15 (7.5)	23 (9.2)				
Marital status				< 0.0001	0.09	< 0.0001	0.0004
Never married	19 (7.6)	26 (13.1)	21 (8.4)				
Married	117 (46.8)	99 (49.7)	175 (70.3)				
Separated/Divorced	52 (20.8)	39 (19.6)	24 (9.6)				
Widow	57 (22.8)	29 (14.6)	25 (10.0)				
Cohabiting	5 (2.0)	6 (3.0)	4 (1.6)				
Work Status				0.24	0.28	0.30	0.12
Employed	218 (87.2)	175 (87.9)	226 (90.8)				
Retired	6 (2.4)	1 (0.5)	5 (2.0)				
Unemployed	26 (10.4)	23 (11.6)	18 (7.2)				
Monthly Income				0.004	0.004	0.049	0.10
> 1000 GHc	42 (16.8)	30 (14.9)	56 (22.5)				
500–1000 GHc	88 (35.2)	51 (25.4)	65 (26.1)				
< 500 GHc	84 (33.6)	101 (50.2)	100 (40.2)				
No response	36 (14.4)	19 (9.5)	28 (11.2)				
Cigarette use				0.42	0.70	0.17	0.48
Current cigarette smoking	3 (1.2)	1 (0.5)	1 (0.4)				
Previous cigarette use	14 (5.6)	10 (5.0)	7 (2.8)				
No cigarette use	233 (93.2)	190 (94.5)	242 (96.8)				
Current alcohol use	20 (8.0)	17 (8.5)	8 (3.2)	0.03	0.86	0.02	0.02
Fruit servings/day				0.10	0.34	0.36	0.02
0	15 (6.0)	8 (4.0)	21 (8.4)				
1–2	163 (65.7)	124 (62.3)	169 (67.9)				
> 2	70 (28.3)	67 (33.7)	59 (23.7)				
Vegetable servings				< 0.0001	< 0.0001	0.004	0.04
0–1	67 (27.0)	60 (30.2)	83 (33.3)				
2	134 (54.0)	63 (31.7)	98 (39.4)				
> 2	47 (19.0)	76 (38.1)	68 (27.3)				
Table added salt				0.57	0.90	0.26	0.49
Never	170 (68.5)	139 (69.8)	190 (76.3)				
Rarely	17 (6.9)	11 (5.5)	12 (4.8)				
Occasionally	39 (15.7)	29 (14.6)	28 (11.2)				
Very often	22 (8.9)	20 (10.1)	19 (7.6)				
Regular physical activity	95 (38.0)	45 (22.4)	72 (28.8)	0.001	0.0004	0.03	0.12
Duration of HIV diagnosis mean ± SD (years)	8.6 ± 4.4	1.3 ± 2.6	N/A	< N/A	< 0.0001	N/A	N/A
Nadir CD4 counts							
Current CD4 counts	641.9 ± 331.5	315.9 ± 271.2	N/A	N/A	< 0.0001	N/A	N/A
Duration on Antiretrovirals mean ± SD (years)	7.7 ± 3.6	N/A	N/A	N/A	N/A	N/A	N/A
Proportion suppressed viremia, n (%)	152	10	N/A	N/A	< 0.0001	N/A	N/A
Log Viral load in unsuppressed,	3.54 ± 1.69	4.82 ± 0.96	N/A	N/A	< 0.0001	N/A	N/A
Clinical staging at diagnosis					0.006		
1	73 (30.3)	54 (27.3)	N/A	N/A			
2	52 (21.6)	54 (27.3)	N/A	N/A			
3	91 (37.8)	85 (42.9)	N/A	N/A			
4	25 (10.4)	5 (2.5)	N/A	N/A			
Current ART regimen							
AZT + 3TC + EFZ	63						
AZT + 3TC + NVP	73						
D4T + 3TC + EFZ	21						
D4T + 3TC + NVP	26						
TDF + 3TC/FTC + EFZ	56						
TDF + 3TC/FTC + NVP	2						
2NNRTI + LPV/r	4						

AZT = Zidovudine, 3TC = Lamivudine, FTC = Emtracitabine, TDF = Tenofovir, EFZ = Efavirenz, NVP = Nevirapine, LPV/r = ritonavir-boosted lopinavir; GHc = Ghana cedis, 1USD = 5GHc.

Table 2
Baseline cardiovascular profile of EVERLAST study participants.

Characteristic	HIV on cART (Group A) n = 250	HIV cART Naïve (Group B) n = 201	HIV negative controls (Group C) n = 250	P-value (A vs B vs C)	P-value (A versus B)	P-value (A versus C)	P-value (B versus C)
Systolic BP, mean ± SD	127.4 ± 23.6	115.2 ± 22.8	132.5 ± 23.5	< 0.0001	< 0.0001	0.02	< 0.0001
Diastolic BP, mean ± SD	79.1 ± 13.5	76.2 ± 14.3	83.7 ± 14.4	< 0.0001	0.02	0.0003	< 0.0001
Blood Pressure categories				< 0.0001	0.0003	0.18	< 0.0001
SBP < 120 mmHg &/or DBP < 80 mmHg	103 (41.4)	118 (58.7)	79 (32.0)				
SBP 120–139 &/or DBP 80-89 mmHg	78 (31.3)	56 (27.9)	87 (35.2)				
SBP 140–159 &/or DBP 90-99 mmHg	39 (15.7)	19 (9.4)	49 (19.8)				
SBP ≥ 160 &/or DBP ≥ 100 mmHg	29 (11.6)	8 (4.0)	32 (13.0)				
Proportion with Hypertension, n (%)	92 (36.9)	47 (23.4)	111 (44.9)	< 0.0001	0.002	0.08	< 0.0001
Proportion of HPT on Rx, n (%)	37 (40.2)	21 (44.7)	33 (29.7)	0.13	0.61	0.12	0.07
Proportion controlled on HPT Rx, n (%)	11 (29.7)	9 (42.9)	15 (45.5)	0.36	0.31	0.17	0.85
Hemoglobin A1c, mean ± SD	5.4 ± 1.1	5.5 ± 0.9	5.4 ± 1.1	0.53	0.69	0.48	0.26
Proportions with HBA1c cut-off				0.53	0.73	0.21	0.65
HBA1c < 5.7%, n (%)	168 (67.5)	142 (70.6)	182 (74.6)				
HBA1c 5.7–6.4%, n (%)	64 (25.7)	48 (23.9)	50 (20.5)				
HBA1c > 6.5%, n (%)	17 (6.8)	11 (5.5)	12 (4.9)				
Proportion with DM	21 (8.4)	19 (9.5)	17 (7.0)				
Total cholesterol, mean ± SD	5.0 ± 1.3	5.4 ± 1.4	5.1 ± 1.3	0.003	0.0009	0.39	0.01
Total cholesterol ≥ 5.2 mmol/l	108 (43.4)	112 (53.6)	108 (44.1)	0.02	0.009	0.87	0.01
LDL-Cholesterol, mean ± SD	3.0 ± 1.1	3.3 ± 1.0	3.1 ± 1.1	0.04	0.01	0.27	0.14
LDL-Cholesterol ≥ 3.4 mmol/l	94 (37.8)	91 (45.3)	98 (40.0)	0.26	0.11	0.61	0.26
HDL-Cholesterol, mean ± SD	1.3 ± 0.5	1.4 ± 0.5	1.4 ± 0.4	0.03	0.01	0.09	0.30
HDL-Cholesterol ≤ 1.03 mmol/l	82 (32.9)	45 (22.4)	59 (24.1)	0.02	0.01	0.03	0.67
Triglyceride, mean ± SD	1.4 ± 0.9	1.5 ± 1.2	1.3 ± 0.7	0.03	0.53	0.03	0.01
Triglyceride ≥ 1.7 mmol/l	62 (24.9)	57 (28.4)	42 (17.1)	0.01	0.41	0.03	0.005
Dyslipidemia, n (%)	198 (79.5)	167 (83.1)	180 (73.5)	0.04	0.34	0.11	0.02
On Statin therapy, n (%)	0 (0.0)	0 (0.0)	0 (0.0)				
Serum creatinine (umol/l), mean ± SD	74.0 ± 88.2	68.8 ± 23.1	74.6 ± 54.1	0.58	0.42	0.93	0.16
eGFR, mean ± SD	84.7 ± 10.6	84.7 ± 11.5	84.0 ± 12.8	0.75	0.99	0.51	0.54
eGFR cut-offs				0.04	0.09	0.02	0.48
> 89 ml/min	167 (67.6)	153 (76.1)	182 (74.3)				
88–60 ml/min	74 (30.0)	42 (20.9)	50 (20.4)				
< 60 ml/min	6 (2.4)	6 (3.0)	13 (5.3)				
Body Mass Index, mean ± SD	27.1 ± 5.5	24.5 ± 5.1	28.2 ± 5.4	< 0.0001	< 0.0001	0.02	< 0.0001
BMI Categories				< 0.0001	0.0009	0.03	< 0.0001
BMI < 18.5 kg/m^2	6 (2.4)	17 (8.5)	3 (1.2)				
BMI 18.5–24.9 kg/m^2	99 (40.1)	99 (49.3)	71 (28.7)				
BMI 25.0–29.9 kg/m^2	75 (30.4)	52 (25.9)	87 (35.2)				
BMI > 30 kg/m^2	67 (27.1)	33 (16.4)	86 (34.8)				
Waist-to-Hip ratio, mean ± SD	0.88 ± 0.09	0.88 ± 0.07	0.91 ± 0.06	< 0.0001	0.57	0.0002	< 0.0001
WHR, raised, n (%)	154 (61.8)	134 (66.7)	193 (78.2)	0.0003	0.29	< 0.0001	0.007
WHR categories				< 0.0001	0.35	< 0.0001	< 0.0001
≤0.90 (low risk)	166 (66.7)	138 (69.0)	111 (44.9)				
0.91–0.96 (moderate risk)	47 (18.9)	42 (21.0)	97 (39.3)				
> 0.97 (high risk)	36 (14.4)	20 (15.8)	39 (15.8)				
Common carotid IMT, mean ± SD (mm)	0.867 ± 0.198	0.869 ± 0.174	0.856 ± 0.189	0.73	0.92	0.53	0.46
Internal carotid artery IMT	0.822 ± 0.186	0.819 ± 0.183	0.822 ± 0.193	0.98	0.84	0.99	0.85
Metabolic syndrome, n (%)	95 (38.2)	65 (32.3)	98 (39.7)	0.25	0.20	0.73	0.11

independently associated with sub-clinical atherosclerosis in adjusted analyses (not shown). Among PLWH on cART, higher total cholesterol was associated with higher odds of outcome measure at 1.26 (95% CI of 1.02–1.55) while among PLWH cART naïve, having severer clinical disease stage 4 compared with stage 1 was associated with odds ratio of 0.09 (95% CI of 0.01–0.87). (Table 3).

3.4.1. Sensitivity analysis

Using a higher common carotid IMT cut-off of ≥1.0mm [30], the proportions were 53 (21.2%) among PLWH on cART, 43 (21.4%) among PLWH cART naïve and 54 (21.6%) in the HIV negative group. In bivariate logistic regression among the PLWH on cART group, the only significant factor associated with CIMT > 1 mm was having a viral load > 50 copies/ml with odds ratio of 1.98 (1.03–3.83), p = 0.04. None of the demographic, lifestyle, cardiovascular, and HIV related factors was significantly associated CIMT > 1 mm in the PLWH cART naïve group. Upon combining the two PLHW groups, only systemic arterial hypertension was significantly associated with CIMT > 1 mm with odds ratio of 1.66 (1.00–2.80), p = 0.05. (Table 4). Compared with optimal blood pressure reading of systolic BP < 120 mmHg and/or diastolic BP < 80 mmHg, having a SBP 140–159 mmHg and/or DBP 90-99 mmHg was associated with an odds ratio of 1.40 (95% CI of 1.02–1.93), $p = 0.04$. Use of protease inhibitor based cART was not associated with higher odds of carotid atherosclerosis in either primary or sensitivity analyses (Tables 3 and 4).

4. Discussion

We have assessed the burden of subclinical atherosclerosis and prevalence of vascular risk factors among Ghanaian PLWH on lifelong cART in an urban tertiary medical center compared with cART naïve PLWH and HIV negative community dwelling controls. Overall, the mean CIMT did not differ significantly among the three study groups, who were all 30 years or older. Using a CIMT cut-off of ≥0.78 mm, we found a high prevalence of subclinical atherosclerosis of 68% among PLWH on cART, 67% among PLWH not on cART and 62% in HIV negative controls. There was also a preponderance of serum lipid abnormalities with a gradient that significantly declined from 83% in PLWH not on cART, to 80% in PLWH on cART, and 74% among HIV negative controls, p = 0.04. Of interest, raised serum total cholesterol

Table 3
Factors associated with Common Carotid Intimal Media Thickness ≥ 0.78 mm among PLWH.

Factors	HIV on combination ART		HIV ART naive		Entire HIV cohort	
	Unadjusted OR	p-value	Unadjusted OR	p-value	Unadjusted OR	p-value
Male	0.85 (0.43–1.67)	0.64	0.67 (0.32–1.39)	0.28	0.76 (0.46–1.25)	0.28
Age	1.00 (0.97–1.03)	0.82	0.98 (0.95–1.01)	0.27	0.99 (0.97–1.01)	0.38
Urban residence	1.14 (0.64–2.00)	0.66	1.08 (0.54–2.17)	0.82	1.11 (0.72–1.72)	0.64
Viral load > 50cpml	1.05 (0.58–1.87)	0.88				
Log viral load			1.12 (0.88–1.43)	0.37	1.00 (0.90–1.13)	0.89
CD4 Counts < 200	1.05 (0.56–1.94)	0.89	1.09 (0.40–2.95)	0.85	1.04 (0.64–1.68)	0.88
WHO Stage (ref. stage 1)						
Clinical stage 2	0.58 (0.27–1.26)	0.17	0.72 (0.31–1.65)	0.44	0.64 (0.36–1.13)	0.64
Clinical stage 3	0.61 (0.31–1.22)	0.16	0.69 (0.33–1.48)	0.34	0.65 (0.39–1.08)	0.09
Clinical stage 4	0.59 (0.22–1.57)	0.29	**0.09 (0.01–0.87)**	**0.04**	0.45 (0.20–1.03)	0.06
Protease inhibitor	0.46 (0.27–1.26)	0.45	N/A		N/A	
Hypertension	1.27 (0.73–2.24)	0.40	1.53 (0.73–3.20)	0.26	1.37 (0.88–2.12)	0.17
Diabetes mellitus	1.13 (0.38–3.33)	0.82	1.32 (0.86–2.02)	0.20	2.30 (0.86–6.18)	0.09
Total Cholesterol	**1.26 (1.02–1.55)**	**0.03**	1.08 (0.88–1.34)	0.12	**1.16 (1.00–1.35)**	**0.049**
LDL Cholesterol	1.15 (0.89–1.48)	0.30	0.94 (0.70–1.24)	0.65	1.04 (0.86–1.26)	0.66
HDL Cholesterol	1.62 (0.88–2.98)	0.13	0.62 (0.34–1.13)	0.12	1.01 (0.67–1.51)	0.98
Triglycerides	1.42 (0.96–2.10)	0.08	1.24 (0.86–1.77)	0.25	**1.32 (1.01–1.73)**	**0.044**
Serum creatinine	1.00 (0.99–1.01)	0.96	1.01 (0.99–1.02)	0.40	0.99 (0.99–1.01)	0.73
Any cigarette use	1.30 (0.40–4.31)	0.66	0.57 (0.17–1.93)	0.36	0.85 (0.38–1.89)	0.52
Waist to Hip ratio	0.79 (0.40–4.31)	0.55	0.97 (0.32–2.96)	0.26	0.80 (0.40–1.59)	0.52
Daily fruit servings	0.93 (0.72–1.19)	0.55	0.98 (0.73–1.33)	0.91	0.93 (0.76–1.14)	0.49
Daily vegetable servings	1.01 (0.74–1.39)	0.94	0.88 (0.67–1.16)	0.36	0.93 (0.76–1.14)	0.51

Bold represents p-values that reach statistical significance

and triglyceride were both associated with an increased risk of carotid atherosclerosis among entire cohort of PLWH. Furthermore, we observed that PLWH with hypertension were more likely to have a CIMT cut-off of ≥1.00 mm which could confer a higher risk of CVDs. Significantly, persistent viremia among HIV-infected patients on cART was also associated in unadjusted analysis with a CIMT cut-off of ≥1.00 mm, indicating that virologic failure if not detected may further heighten the risk of CVD co-morbidity in addition to AIDS related events.

Our findings agree with those of a large US based HIV collaborative study comprising of a cross-section of 5 cohorts of > 1000 HIV-infected and 500 HIV-uninfected controls where the investigators found CCA-IMT values among HIV-infected individuals aged 30 to 75 years were similar to or lower than those in HIV-uninfected participants [31]. Two previous investigations among indigenous Africans using a similar CIMT cut-off value of ≥0.78 mm reported significantly lower subclinical atherosclerosis rates of 14% among cART naïve and 24% among cART exposed Ugandans [22] and 12% in South Africans [23] compared with our findings. We found no differences in CIMT among Ghanaian PLWH compared with age-and sex-matched HIV negative controls. However, in the aforementioned African studies [22,23], there were no HIV negative groups hence limiting their ability to determining the prevalence of subclinical atherosclerosis among PLWH relative to an HIV uninfected group in the African context. One report from

Table 4
Factors associated with Common Carotid Intimal Media Thickness > 1 mm among PLWH (Sensitivity analysis).

Factors	HIV on combination ART		HIV ART naive		Entire HIV Cohort	
	Unadjusted OR	p-value	Unadjusted OR	p-value	Unadjusted OR	p-value
Male	0.87 (0.39–1.95)	0.74	0.72 (0.26–2.03)	0.54	0.70 (0.37–1.31)	0.26
Age	1.00 (0.97–1.04)	0.87	1.00 (0.96–1.04)	0.98	1.00 (0.98–1.03)	0.89
Urban residence	0.91 (0.48–1.73)	0.76	1.03 (0.45–2.28)	0.95	0.97 (0.98–1.03)	0.90
Duration of HIV diagnosis	0.98 (0.90–1.07)	0.72	1.02 (0.90–1.16)	0.72	0.99 (0.95–1.04)	0.75
Viral load > 50cpml	**1.98 (1.03–3.83)**	**0.04**	1.23 (0.25–5.89)	0.79	1.41 (0.86–2.31)	0.17
Log viral load			1.04 (0.77–1.40)	0.81		
CD4 Counts < 200	1.26 (0.44–3.65)	0.67	1.57 (0.78–3.17)	0.21	1.38 (0.81–2.33)	0.24
WHO Stage (ref. stage 1)						
Clinical stage 2	0.94 (0.39–2.23)	0.89	0.78 (0.30–1.99)	0.60	0.86 (0.45–1.62)	0.63
Clinical stage 3	0.80 (0.38–1.73)	0.58	1.12 (0.50–2.52)	0.78	0.95 (0.55–1.66)	0.87
Clinical stage 4	1.11 (0.38–3.23)	0.85	0.00	0.00	0.87 (0.32–2.33)	0.78
Protease Inhibitor	1.24 (0.13–1.73)	0.86	N/A		N/A	
Hypertension	1.53 (0.80–2.95)	0.20	2.04 (0.84–4.95)	0.11	**1.66 (1.00–2.80)**	**0.05**
Diabetes mellitus	1.12 (0.35–3.59)	0.85	2.20 (0.61–7.89)	0.23	1.48 (0.63–3.46)	0.37
Total Cholesterol	1.16 (0.92–1.47)	0.20	0.87 (0.68–1.12)	0.28	1.01 (0.86–1.20)	0.86
LDL Cholesterol	1.21 (0.90–1.61)	0.21	1.00 (0.72–1.39)	0.99	1.11 (0.90–1.37)	0.34
HDL Cholesterol	1.24 (0.68–2.26)	0.48	0.83 (0.41–1.71)	0.62	1.04 (0.66–1.65)	0.85
Triglycerides	1.12 (0.84–1.50)	0.43	0.81 (0.52–1.52)	0.34	0.98 (0.78–1.22)	0.85
Serum creatinine	1.00 (0.99–1.02)	0.46	1.00 (0.72–1.39)	0.99	1.00 (0.99–1.01)	0.57
Any cigarette use	1.15 (0.36–3.70)	0.81	0.46 (0.06–3.69)	0.46	0.80 (0.29–2.15)	0.65
Waist to Hip ratio	0.23 (0.01–7.85)	0.42	1.04 (0.77–1.40)	0.73	0.28 (0.02–5.03)	0.39
Daily fruit servings	1.05 (0.79–1.41)	0.73	0.93 (0.65–1.31)	0.66	1.00 (0.80–1.25)	0.99
Daily vegetable servings	1.09 (0.77–1.56)	0.62	0.90 (0.66–1.24)	0.53	0.98 (0.78–1.24)	0.88

Bold represents p-values that reach statistical significance

Ethiopia included HIV uninfected controls and found no significant differences in Carotid IMT among the PLWH on cART, PLWH cART naïve and HIV negative participants [32]. This notwithstanding, our high rate of sub-clinical carotid atherosclerotic disease agree more closely with that of a Spanish cohort of HIV patients with a prevalence of 65% using a comparable CIMT cut-off of 0.80 mm [33]. A meta-analysis of observational studies demonstrated a modest increment in CIMT of +0.04 mm among PLWH over that among HIV negative controls [34]. We observed a rather subtle mean difference of +0.013 mm and + 0.011 mm respectively between PLWH on cART and PLWH not on cART relative to HIV negative controls.

Cross-sectional and prospective studies conducted in High Income Countries (HICs) have demonstrated associations between HIV infection and its treatment with carotid atherosclerosis [17–20]. These associations however have not been consistently corroborated by other studies, particularly those from low-and-Middle Income countries such as Brazil [35]. Reasons for these inconsistencies may be due differences in methodological assessments of CIMT outcome measures. For instance, different studies have used different cut-off's of CIMT such as 0.78 mm [22,23], 0.80 mm [33], 0.90mm [36], and 1.0mm [30] to define subclinical atherosclerosis giving rise to differences in prevalence rates. In the present study, we analyzed prevalence and predictors of carotid atherosclerosis using two CIMT cut-off's viz 0.78 mm and 1.00 mm. To minimize errors in measurements of CIMT, we applied the robust Mainheim consensus protocol [27] and had measurements performed independently by two experienced sonographers using an automated edge detection reading system. From an epidemiological perspective, the higher rates of atherosclerosis in PLWH from HICs have been associated with a preponderance of male gender, older age of PLWH, cigarette smoking, and use of protease inhibitor-based cART. This contrast with the scenario in SSA where HIV epidemiology is characteristically dominated by female preponderance, low cigarette smoking rates, and use of NNRTI-based cART as first line therapy compared with protease inhibitor as captured in our study. Indeed, Maggi and co-investigators [30] showed clearly in an Italian cohort that, PLWH on protease inhibitors based cART had significantly higher burden of subclinical atherosclerosis (52.4%) compared with those on NNRTI-based cART (15.2%) and that the rate of CIMT abnormalities were non-significantly different between those on NNRTI-based cART and HIV negative Italian controls (14.3%). To position our results in its proper context, it is important to acknowledge that study population comprised of adults aged > 30 years and could explain the overall higher prevalence of carotid atherosclerosis compared with other studies from SSA. Overall, the body of scientific literature suggests moderate but significant association between HIV infection and risk of subclinical atherosclerosis with occurrence of CVDs [37] and CVD-related deaths [38] compared with HIV negative controls. However, the contribution of traditional vascular risk factors in the HIV population appear to be significant determinants of CVD risk compared with HIV-specific factors.

These traditional vascular risk factors were rife in our study population and its convergence in PLWH is projected to lead to a rise in CVD comorbidity. Approximately 80% of PLWH in Ghana had perturbations in routinely measured lipid sub-fractions relative to 75% among HIV negative controls suggesting a heightened risk of dyslipidemia induced by HIV infection against a backdrop of high baseline prevalence of lipid abnormalities in the community. None of the study participants were receiving lipid-modifying therapy because lipid panels are not routinely ordered as part of care for PLWH and cost of treatment of dyslipidemia is borne by out-of-pocket payments by patients in our setting. Dyslipidemia, a potent but neglected risk factor for atherosclerotic CVDs in SSA [39], has recently been found to be the second leading risk factor for stroke occurrence among young West Africans in Ghana and Nigeria [40,41]. The fact that dyslipidemia rates are substantial even among cART naïve PLWH should alert clinicians to the unmet but growing need for CVD risk mitigation across the spectrum of clinical care for PLWH in resource-limited settings. Indeed, chronic immune activation and inflammation engendering atherosclerosis, has been well characterized even among virologically suppressed HIV-infected patients receiving cART [20]. A recent meta-analysis found a modest reduction in all-cause mortality with statin use among PLWH [42]. This salutary effect of statin therapy among PLWH would require widespread adoption after trials have been piloted in SSA to assess the feasibility, efficacy, and cost-effectiveness of such intervention in a region coping with a double burden of communicable and non-communicable diseases.

The burden of hypertension was significantly higher among PLWH on cART (37%) compared with PLWH not on cART (23%) but rates were overall higher among HIV negative controls (45%) with less than half of hypertensive patients receiving antihypertensive medications. Hypertension among PLWH was associated with a higher odds of subclinical atherosclerosis using a CIMT cut-off > 1 mm, perhaps highlighting the potentiating effect of blood pressure on subclinical atherosclerosis. Our previous studies have highlighted profound challenges in hypertension and diabetes control even in health facilities across Ghana [43–46]. Therefore in HIV programs in Africa where CVD risk management is not coupled with the HIV care package comprising of antiretroviral therapy and treatment of opportunistic infections, PLWH are at high risk CVD morbidity and mortality. While we cannot recommend routine carotid Doppler for all PLWH across Africa, screening and management of known vascular risk factors such as hypertension, dyslipidemia, diabetes, obesity, and poor lifestyle habits such as alcohol use, cigarette smoking, and eating patterns require closer attention towards mitigation of CVD risk in PLWH. There is also a need for increased advocacy for policy change recommendations to support the integration of CVD care and coverage for treatment of CVD risk factors among PLWH.

On broader scope, the high rates of uncontrolled vascular risk factors detected among community dwelling HIV sero-negative controls is a cause for concern. The fact that among a predominantly young adult population, we found approximately 74% with dyslipidemia, 45% with hypertension, 25% had either pre-diabetes or diabetes mellitus, and 40% had metabolic syndrome portends grave consequences given that majority were unaware of the presence and relevance of having these vascular risk factors. None of these representative control subjects from the community were receiving treatment for dyslipidemia and the minority on antihypertensive treatment for hypertension was also poorly controlled. With such high rates of uncontrolled modifiable cardio-metabolic risk factors in the general population, nearly 6 out of 10 adults had abnormal carotid intimal medial thickening, which is a potent harbinger of strokes and ischemic heart disease. An aggressive and concerted public health approach to the control of these vascular risk factors should become an urgent priority for the Ministry of health in Ghana and certainly in other LMICs in Africa to avert the catastrophic outcomes of cardiovascular diseases observed in these regions [47–52].

In cross-sectional studies, associations between factors and outcomes are evaluated hence no causal inferences can be drawn from our study findings. A prospective study to evaluate causal factors associated with occurrence and progression of subclinical atherosclerosis, and CVD outcomes may be justified on the basis of the findings from our present study. Our inclusion criterion was an age cut-off of 30 years and above to improve our yield of adults at higher risk of CVD. The exclusion of individuals below this age cut-off could explain why the mean CIMT was higher than those reported from other studies from SSA [22,23]. It would be important to consider the barriers and facilitators of CVD risk management in a resource-limited setting in qualitative studies in order to design culturally attuned interventions to tackle the growing burden of CVDs. We are currently analyzing qualitative data from the EVERLAST study to further enrich our understanding of the unique sociocultural indicators in the SSA context influencing CVD risk control in PLWH.

In conclusion, we have found a high baseline prevalence of uncontrolled CVD risk factors in the Ghanaian population with a modest accentuation by the pro-atherogenic effects of HIV infection and its treatment. Patient-level and systemic-level interventions are urgently needed to address these gaps in the control of CVD risk factors in PLWH.

Conflicts of interest

None.

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