HIV, Cardiovascular Disease Risk Factors, and Subclinical Atherosclerosis among Kenyan Adults

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Abstract

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Introduction

Greater carotid intimal media thickness (CIMT) and presence of carotid plaque have been validated as measures of subclinical atherosclerosis. HIV is a risk factor for cardiovascular disease (CVD) and has been associated with higher CIMT in North America and Europe. In Sub-Saharan Africa (SSA), there are more people living with HIV (PLHV) on antiretroviral therapy (ARV) and the association of HIV status and CVD risk factors with CIMT has not been well studied. We evaluated these factors in a cohort of PLHV and HIV negative individuals in Western Kenya.

Methods

In this cross-sectional study, a sub-cohort of 145 PLHV on ARV (≥6 months) and 117 HIV-negative adults accessing community-based services at Kisumu County hospital, underwent bedside measurement of CIMT using carotid ultrasound. Using simple and multivariable linear regression analyses, we examined associations between traditional cardiovascular risk factors,

carotid plaque, and mean CIMT, amongst the sub-cohort and then stratified by HIV status. Amongst PLHV, we examined the association between CIMT and HIV related factors, including viral load and CD4 count.

Results

The HIV negative group had a higher prevalence of several traditional CVD risk factors including older age ≥ 55years (p =0.002), history of hypertension (HTN) (p=0.02), hypertension treatment (p = 0.03) and elevated blood pressure (BP) (p = 0.01). The overall mean CIMT in the cohort was 0.42mm (standard deviation [SD] 0.12), and lower in PLHV (0.41mm [SD 0.12] vs HIV negative (0.44mm [SD 0.14], p = 0.02). After adjustment for significant variables in the multivariable regression model, HIV status was not significantly associated with greater mean CIMT (p = 0.19). In the multivariable regression models, amongst PLHV, those with elevated blood pressure or hypertension treatment had a 0.06mm higher mean CIMT (95% confidence interval [CI]; 0.02,0.11, p = 0.002). In the HIV negative group, older age (0.07mm [95%CI; 0.02,0.12] p = 0.006), high total cholesterol (TC) (0.09mm[95%CI: 0.03,0.14] p = 0.01) and diabetes (0.17mm [95%CI:0.03, 0.31] p= 0.02) were associated with higher mean CIMT. The overall prevalence of carotid plaque was low (15/262 [6.0%]), and not significantly different between the two groups (p =0.71). HIV related factors such as CD4 count, viral load, and ARV regimen were not associated with greater CIMT in the simple linear regression models.

Conclusion

We found no significant association with HIV positive status and subclinical atherosclerosis. When stratified by HIV status, PLHV had fewer CVD risk factors associated with CIMT and HIV- related factors were not significantly associated with CIMT.

I.0 Introduction

Human Immunodeficiency Virus (HIV) has been associated with up to two-fold higher risk of cardiovascular disease (CVD) (1, 2). This is likely due to increased chronic inflammation and immune activation associated with HIV infection (3) as well as secondary to antiretroviral medication (ARVs), in particular protease inhibitors (PIs)(1, 4). In sub-Saharan Africa (SSA) there are now more people living with HIV (PLHV), and given the large and increasing burden of cardiovascular disease in SSA, there is a need for clinical tools to improve risk stratification and management of CVD for PLHV. Clinical tools that are reliable, feasible and cost effective are needed.

In longitudinal studies in the United States and Europe, greater carotid artery intimal media thickness (CIMT) has been validated as an indicator of subclinical atherosclerosis, and as a predictor for future CVD events, namely stroke and myocardial infarction (MI) (5,6). Carotid plaque, a focal lesion in the artery wall which can impede blood flow, is also recognized as a marker of subclinical atherosclerosis and an independent predictor of cardiovascular disease (CVD) independent of CIMT (7). CIMT thickness varies by age, race, and sex, but carotid plaque may still be present even when CIMT is not increased (8,9,10). Both CIMT and the presence of carotid artery plaque may be assessed non-invasively, using ultrasound. This provides an advantage for screening for the presence of subclinical CVD over more invasive and costly procedures such as coronary angiography.

In a large meta-analysis and systematic review of observational studies among PLHV, higher CIMT has been shown to be associated with HIV positive status (11) However, most of these studies have been from countries with a low HIV prevalence, such as Europe or North America, and greater use of protease inhibitors (PIs) compared to other ARVs (11,12). In the small number

of studies from SSA, the association between HIV positive status and higher CIMT has not been uniformly demonstrated. Given the higher prevalence of HIV in SSA as well as the differing interaction between genetic and environmental factors that confer risk for CVD, more work is needed to determine the relationships between abnormal CIMT, HIV, and traditional CVD risk factors in SSA.

In this study we evaluated the association between HIV status and CIMT in a higher prevalence HIV setting in Western Kenya. We also examined associations between traditional cardiovascular risk factors, carotid plaque, and CIMT, when stratified by HIV status. Finally, amongst PLHV, we examined the association between CIMT and HIV related factors, such as viral load and CD4 count.

2.0 Methods

2.1. Study design and setting

This study enrolled HIV positive and HIV negative men and women living in Western Kenya and was conducted as a collaboration between the University of Washington (UW), University of Nairobi, Kenyatta National Hospital and the Kenyan Ministry of Health. Participants were enrolled at Kisumu Sub-county Hospital in Kisumu County and surrounding communities in Western Kenya. By design, the study enrolled 150 HIV-positive men; 150 HIV-positive women; 149 HIV negative men; and 149 HIV negative women. Eligibility criteria included being at least 30 years of age and living within a 50 km radius of the hospital. Those with HIV had to be enrolled and regularly attending the HIV Comprehensive Care Clinic (CCC) and using antiretroviral treatment (ART) for a minimum of 6 months.

Human subject approval was obtained from the University of Washington Institutional Review Board (IRB) in the US and from the Kenyatta National Hospital (KNH)/University of Nairobi (UoN) Ethical and Scientific Review Committee in Kenya. All participants provided written informed consent.

2.2 *Study procedures*

This was a cross-sectional study and detailed study procedures have previously been published (13). In brief, subject health and demographic data were collected through a modified WHO STEPS questionnaire (14); physical examination, including anthropometric measurements; laboratory testing; and medical chart abstraction. Participants returned following an initial visit for carotid ultrasound and blood draw if not fasting.

CIMT ultrasound examination: Radiographers at Kisumu Sub-county Hospital received training in both scanning technique, acquisition and interpretation of images on the Sonosite M Turbo ultrasound machine (FUJIFILM, Sonosite Inc, Bothell) using a HFL38X / 13-6 MHZ transducer. The training and quality assurance of radiographers was provided by Dr. Faith Ameda, a radiologist experienced in performing carotid ultrasound and measurement of CIMT for research purposes (15). Standard operating procedures for this study were based upon protocols for measurement of CIMT from the American Society of Echocardiography (ASE) (16). The Sonosite Software program (SonoCalc V5.0.0.12) was used for image acquisition and reporting.

The study participant was positioned in the semi upright position with the head slightly tilted to the left or right, depending on the side being examined. All study participants underwent examination of the extracranial carotid arteries, identification of carotid plaque and measurement of carotid intimal media thickness (CIMT), on both right and left common carotid arteries. The

common carotid artery (CCA) was identified with the ultrasound probe in the longitudinal position using the proximal point 10mm from the carotid bulb. Measurements were taken of the intima medial thickness with the ultrasound probe in the anterior, posterior and lateral position and three measurements of the mean IMT segment, calculated automatically by the software, were made at the near and far wall (six in total) in each position. For each side an overall average, minimum and maximum CCA, and mean IMT were calculated, as well as the overall combined average, minimum, and maximum for all the measurements. The combined average CCA mean IMT was used in this study as it represents the overall average and was used in another SSA study by study investigators (15).

Ultrasound images for each participant were recorded, stored, and transferred offsite after each examination. Subsequent reporting was done by the research radiologist and a formal report generated on the SonoCalc V50.0.12. To minimize inter-reader error, all reports were interpreted by the one research radiologist. Data management was carried out by a program assistant from the International AIDS Research and Training Program (IARTP) in Seattle.

2.4. Dependent and independent variables

CIMT was analyzed as a continuous variable and was relatively normally distributed. Independent variables included demographic and lifestyle factors; age (<55 vs ≥55 years), sex, smoking status (current defined as within 12 months and ex-smoker after 12 months) and education level (less than or equal to and greater than secondary level). CVD history included prior diagnosis of hypertension, hypertension treatment and diabetes treatment, and prior myocardial infarction (MI) or stroke (CVA). Anthropometric measurements included body mass index (BMI) (<25 or ≥25kg/m^2), abdominal obesity (female>88cm and males >94cm), high blood pressure (BP); a

systolic BP ≥140mmHg or diastolic BP ≥90mmg or treatment for hypertension (HTN), as per the World Health Organization recommendations (17). Laboratory measurements included were elevated total cholesterol (TC) >200mg/dl, elevated low density lipoproteins (LDL-C) >130mg/dl, reduced high density lipoproteins (HDL-C) (for females <50mg/dl and for males <40mg/dl) and elevated triglycerides (TG) >150mg/dl, as per the criteria used for Metabolic syndrome (MetS) (18). Diabetes was defined as a fasting blood glucose level ≥126mg/dl (19) as per WHO recommendation. HIV status was an independent variable as well as duration of antiretroviral therapy (years), current CD4 count (cells/mm^3), nadir CD4 count (cells/mm^3), suppressed viral load (<1000 copies/ml) and undetectable viral load (<50 copies/ml) and ARV regimen (either a protease/first line vs non-protease inhibitor/second line regimen).

2.5 Statistical analysis and sample size

Baseline characteristics of the cohort were summarized and compared between HIV positive and negative individuals using the Mann U Whitney test for median values and student t test for continuous variables. Chi squared or Fisher's exact test were used to compare frequencies for categorical variables. The association between independent variables and CIMT was explored via simple linear regression models, first with the entire cohort and then separately with the HIV positive and HIV negative group. In the multivariable regression model, those independent variables with a p value of ≤ 0.15 in the simple linear regression model were included, as well as those variables of clinical significance that *a priori* included age, sex, and education status. The multivariable model was conducted with backwards regression and stepwise removal variables until the best model fit was obtained. A p value of 0.05 was considered statistically significant. All statistical analysis was conducted using R software version 3.5.2 (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA).

This study was powered to detect a minimum mean CIMT difference of 0.04 mm with 80% confidence enrolling a minimum of 110 HIV-positive participants and 110 HIV-negative participants. The reference mean difference in CIMT has been used in previous studies (14) as well as in from the Fat Redistribution and Metabolic Changes in HIV infection (FRAM) study (2), a 5 year longitudinal US study examining cardiovascular risk in a large HIV positive cohort using CIMT. Not all the participants had a formal report generated by the research radiologist assigned to the study, due to time limitations. Following data management, only 262 participants had a report verified and used in the final analysis, however we calculated this study was still adequately powered to detect significant differences in CIMT.

3.0 Results

3.1 Demographic and clinical characteristics

Of the 262 participants, 145 were HIV positive and 117 were HIV negative (Table 1). The proportion of those ≥ 55 years was lower in the PLHV group than in the negative group, 40% vs 59% respectively (p= 0.02). Females comprised over half of the PLHV group and less than half of the HIV negative group; 56% vs 46% (p = 0.12). The proportion reporting secondary education or above in both groups was similar, 40% vs 42% (p =0.76).

Few participants had established cardiovascular disease; overall only 3% of participants reported prior stroke or myocardial infarction. Approximately 10% in the PLHV group reported a prior diagnosis of hypertension compared to 21% in the HIV negative group (p =0.02), however, few in either group reported taking an anti-hypertensive agent (3% vs 8%; p = 0.09). Only one participant reported taking aspirin and no participant was taking a statin. The use of tobacco products

(cigarettes, manufactured or hand rolled, cigars, waterpipes [shisha] or pipes [kiko]) in the last 12 months was low, with only 3% among PLHV and 7% in the HIV negative group reporting use (p =0.24). The proportion of those reporting past use of tobacco products in each group was also similar: 11% in PLHV and 13% in the HIV negative group (p =0.33).

Hypertension and obesity are well-described CVD risk factors. The proportion of participants with elevated blood pressure, defined as either systolic ≥140mmHg and/or diastolic ≥90mmHg was higher in the HIV negative group compared to PLHV (p = 0.02). Approximately a third in each group had a BMI ≥25kg/m^2 (p = 0.65) and were classified as overweight or obese. The proportion of participants with abdominal obesity, defined as waist circumference of >94cm in males and >88cm in females, was 23% in the PLHV group and 28% in HIV negative group (p = 0.39).

With respect to laboratory measurements, less than a third of participants had dyslipidemia. There was no significant difference in the proportion of participants with elevated TC between PLHV and HIV negative participants (23% vs 25%, p = 0.84), elevated LDL-C (16% vs 23%, p = 0.22), and reduced HDL-C for both females (26% vs 31%. p = 0.66) and males (19% vs 26%, p = 0.32). However, there was a statistically significant difference in the proportion with elevated TG between the PLHV and HIV negative group (12.9% vs 4.7%, p = 0.03). There was no statistically significant difference in the proportion with diabetes and the numbers were very low (1.4% vs 3.7%, p =0.41). Only 2 participants reported taking diabetes treatment in the HIV positive group; including insulin (1) and an oral agent (1).

Among HIV positive participants, median duration on ART was 9.0 years (interquartile range [IQR] 4.0-11.0). Median CD4 count was 489.0 cells/mm^3 (IQR 343.0-654.0). Median nadir CD4 count was 372 cells/mm^3 (IQR 215-546). All 139 participants with samples available were virally suppressed, defined as viral load <1000 copies/ml. Approximately 80% had undetectable viral

load, defined as <50 copies/ml, and 121 (84.0%) were on a first line or non-protease inhibitor (non-PI) regimen, with 24 (16%) on a 2nd line or protease inhibitor (PI) regimen.

3.2 Carotid plaque and CIMT

The overall mean CIMT in the cohort was 0.42mm (standard deviation [SD] 0.12), The mean CIMT was lower in PLHV than in the HIV negative group (0.41mm [SD 0.12] vs 0.44mm [SD 0.14], p = 0.02). The prevalence of carotid plaque in the entire cohort was approximately 6% (15/262). Of the 15 participants that had plaque detected on carotid ultrasound, there were nine participants in the HIV positive group and six in the HIV negative group (p =0.71). Plaque was mostly located in the carotid bulb (13/15, 87.0 %). For those with plaque there was a 0.02mm higher mean CIMT compared to those who did not have plaque (95%CI; -0.04,0.08). However, this was not a statistically significant difference (p= 0.53).

3.3 Traditional CVD risk factors and CIMT in the cohort

Simple linear regression analyses: Overall several factors were significantly associated with CIMT in simple linear regression models using data from the entire cohort, and these included older age, higher blood pressure and/or use of an antihypertensive agent, elevated TC, elevated LDL-C and diabetes (Table 2).

In the study cohort, HIV positive status was associated with a 0.05mm lower CIMT (95% confidence interval [CI]; 0.01, 0.07) compared to those who were HIV negative, and this was statistically significant (p = 0.02). Older age, ≥55years, was associated with a 0.05mm higher CIMT (95% CI; 0.01,0.07), compared to those <55 years of age (p = 0.004). Those with elevated blood pressure or hypertension treatment had 0.05mm higher mean CIMT (95%CI; 0.01,0.08) compared to those with normal blood pressure and not on hypertension treatment (p = 0.009).

Those with elevated TC had a 0.03mm higher mean CIMT ([95%CI; -0.01,0.07], p =0.10), and those with elevated LDL-C had a 0.04mm higher mean CIMT, compared to those with a normal range LDL-C ([95%CI; -0.001,0.08], p =0.06), although these both were borderline in terms of statistical significance. Finally, a diagnosis of diabetes was associated with a 0.12mm higher mean CIMT in comparison to those without a diagnosis of diabetes ([95%CI; 0.02,0.22], p = 0.02)

Multivariable analyses[1]*:* Independent variables in the initial model included older age, female sex, secondary education, ex-smoking status, high blood pressure or hypertension treatment, elevated TC, elevated LDL-C and diabetes (Table 2). After regression analysis, HIV positive status was not significantly associated with greater CIMT in the final model (p = 0.19), Significant associations were seen in those who were older with a 0.03mm higher CIMT ([95%CI; 0.001,0.07], p = 0.04). and in those with a diagnosis of diabetes with a 0.11mm higher CIMT, compared to those without diabetes ([95%CI; 0.008,0.21], p = 0.02).

3.5 Traditional CVD risk factors and CIMT stratified by HIV status

*Simple linear regression analyses***:** Amongst PLHV (Table 3), a significant association were seen in those with elevated blood pressure or on hypertension treatment who had a 0.06mm higher CIMT compared to those with a normal range blood pressure or not on treatment (95%CI; 0.02,0.11, p =0.003). None of the HIV related factors had significant associations with CIMT in simple linear regression analysis (Table 3). In the HIV negative group, older age was associated with a 0.07mm higher mean CIMT ([95%CI; 0.02,0.12], p = 0.006) Those with elevated TC had a 0.08mm higher mean CIMT ([95%CI; 0.02,0.14], p = 0.01) and those with an elevated LDL-C had a 0.07mm higher mean CIMT ([95%CI: 0.005,0.13], p= 0.04). Those with diabetes had a 0.17mm higher mean CIMT ([95%CI:0.03, 0.31], p = 0.02).

Multivariable linear regression analyses[2,3]: Among HIV positive participants, independent variables included in the initial model included older age, female sex, secondary school education and high BP or use of hypertension treatment. In the final multivariable model only elevated blood pressure or hypertension treatment was associated with 0.06mm higher mean CIMT ([95%CI; 0.02,0.11], p = 0.002) after adjustment for older age, female sex, and higher educational status. Female sex was not significantly associated with CIMT in this final model (p=0.08). In the HIV negative group, independent variables included in the initial model included older age, female sex, secondary school education, elevated TC, elevated LDL-C, and diabetes. In the final model. those who were older had a 0.07mm higher mean CIMT ([95%CI; 0.02,0.12], p = 0.006), those with elevated TC had a 0.09mm higher CIMT ([95%CI: 0.03,0.14], p = 0.01) and those with diabetes had a 0.17mm higher mean CIMT ([95%CI:0.03, 0.31], p= 0.02).

4.0. Discussion

In this cross-sectional study of Western Kenyan adults, with a virally suppressed group of PLHV and a community matched group of HIV negative individuals, HIV positive status was not associated with higher CIMT after adjustment for other significant CVD risk factors. This has also been observed in several other SSA studies (20,21) but is not consistent with findings from studies in high and middle-income countries that found higher CIMT in PLHV compared to HIV negative adults (22,23). Importantly, we found some traditional CVD risk factors to be associated with higher CIMT; elevated blood pressure, hypertension treatment, elevated TC, and diabetes, and this was true more for HIV negative individuals. Despite the lower values of CIMT in this cohort, this finding helps to confirm that we were accurately measuring CIMT and that the lack of association with HIV status confirms this group is likely at lower risk for subclinical atherosclerosis.

The lack of association between HIV status and greater CIMT has also been observed in studies not only from SSA, but other low middle income countries (LMICs) such as Thailand (24) and Brazil (25). However, there are inconsistencies and some SSA studies have had shown the reverse. A Ugandan study by Muiru et al. (2018) reported a higher mean CIMT (0.68mm) in PLHV compared to HIV negative (0.62mm) and this difference was statistically significant (26). The four center H3 Africa- HW1 Gen Study (21), reported an overall age and sex mean adjusted CIMT of 0.64mm with a statistically different mean CIMT between centers: the highest CIMT at the Ghana site (0.69mm) and lowest in Agincourt, one of the SA sites (0.60mm). The prevalence of HIV in this study varied from <1% to 35%, although in some centers HIV status was self-reported. Overall, positive HIV status was associated with lower CIMT in this study.

These study population mean CIMT measurements are noticeably higher than in our study. In addition, some studies (15, 24, 25) have used a definition of subclinical atherosclerosis as an IMT > 0.78mm; a measurement derived from a European longitudinal study, tracking intimal media thickness of children with familial hypercholesterolemia and healthy comparators (27). However, only a few participants in our study had CIMT thickness of >0.78mm (4/262, 2.0%). The reason for lower overall mean CIMT values in our study is unclear but could reflect better management of cardiovascular risk factors in western Kenya than in other SSA countries, or other lifestyle or environmental factors, but could also be due to differing ultrasound scan technique between studies. Some studies have employed maximum CIMT rather than mean and have also have reported a combination of internal carotid and bulb measurements that may yield higher mean IMT measurements due to smaller lumen and greater turbulence of blood flow with earlier atheromatous changes (28,29).

We observed several cardiovascular risk factors in the cohort to be associated with elevated CIMT in both the simple and multivariable linear regression models that differed when stratified by HIV status. In the original cohort (13), the prevalence of MetS was found to be high overall and greater in HIV negative adults, conferring a great risk of future CVD. In the population included in our study we also observed a greater prevalence of CVD risk factors in the HIV negative group, notably older age, a history of hypertension, hypertension treatment and an elevated blood pressure. In PLHV hypertriglyceridemia was more prevalent. The use of statins and aspirin, the mainstay of primary prevention of CVD in Western countries, was almost non-existent in the cohort.

In terms of association of CIMT between PLHV and HIV negative groups, we observed differing different CV risk factor association with CIMT. In PLHV, elevated blood pressure or hypertension treatment were significantly associated with higher CIMT in the multivariable regression model. In the HIV negative group, older age, high TC, and diabetes were associated with CIMT. These findings have been observed in some SSA studies. A smaller cross-sectional study in Uganda utilizing CVD risk scores and their association with CIMT (26). In this study, HIV negative participants had higher CVD risk scores with higher median systolic blood pressure, current smoking status and higher median CVD risk scores that were associated with high mean CIMT.
A larger cross sectional study by Mosepele et al (2017) in Botswana found among PLHV, older age higher waist hip ratio were associated with higher CIMT compared to the HIV negative groups where older age higher non-HDL cholesterol and higher HBA1c were associated with higher CIMT (20).

Our finding of an association of elevated blood pressure with hypertension treatment in the PLHV group in both the simple and multivariable regression model was interesting given the lower prevalence of self-reported hypertension, and lower prevalence of elevated blood pressure in this group. Smoking prevalence was low, and we did not find a significant difference in the prevalence of higher BMI, central obesity or dyslipidemia between groups, apart from a higher prevalence of hypertriglyceridemia in PLHV. Use of hypertension treatment was lower than in the HIV negative group, a finding that is different than other studies, where PLHV have had lower blood pressure (20, 30), and better hypertension treatment. Of note, the PLHV in this group were older and had a higher median time on ARVs than in the original cohort, but the majority were virally suppressed and on non-PI based regimens. A possible explanation includes that finding that PLHV in SSA may have increased markers of endothelial dysfunction despite longstanding viral suppression (31) which may contribute to higher CIMT in the context of being undertreated for hypertension, although measurement of inflammatory markers such as CRP and IL-6 would further confirm this hypothesis. The other finding of a significant association of diabetes in both the entire cohort and HIV negative study population should be interpreted with caution given the small numbers (1.4% vs 3.7%, $p = 0.41$).

Strengths of this study include the use of an HIV negative comparator group as a baseline to assess the relationship between CVD risk factors on CIMT, use of a single radiologist to provide all CIMT measures, and a community-based cohort. Limitations of this study include the cross-sectional study design which does not permit the analysis of the progression of subclinical atherosclerosis and the effect of treatment of CVD risk factors and HIV disease management. The study was also small although powered appropriately. Our cohort was older than other studies in SSA but CIMT values were lower as was the presence of carotid plaque and this may have been

due to ultrasound technique. Most studies seem to sue similar guidelines for measurement and either cardiologists or radiologists to report images. However, some studies have suggested that measurement of CIMT at the common carotid artery may not be as accurate as at the internal carotid or carotid bulb (20,32, 33) where early atherosclerosis may be detected.

Finally, although CIMT is validated in North America as a surrogate marker of atherosclerosis, newer techniques such as coronary artery calcium scores or ankle brachial index in addition to family history and high sensitivity c- reactive protein (hs-CRP) may also be used to risk stratify subjects. What the most consistent and powerful tool is to quantify CVD risk in SSA will require larger studies with longitudinal follow up and event capture. CIMT, when used in conjunction with traditional markers for CVD may be a useful tool in a LMIC setting but still requires further validation.

5.0. Conclusion

In this small cross-sectional study of middle age to older Western Kenyan adults, we did not observe a significant association of HIV status with subclinical atherosclerosis after adjustment for other known cardiovascular risk factors. We observed a higher prevalence of some CVD risk factors in the HIV negative group and associations between some of these CVD risk factors and CIMT. These findings are similar to several other studies in SSA that observed more significant associations with CVD risk factors and higher CIMT in HIV negative groups and may reflect better access to medical care and support for PLHV.

Our overall CIMT measurements and plaque prevalence were lower than other studies and this may be due to underlying study population factors as well as scan technique. However, variation in study designs and population sampling, differences in the definition of abnormal CIMT and

scanning techniques may make direct comparisons difficult with other studies. These results add to the body of literature and should be confirmed with a larger, longitudinal study.

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7.0 Tables

Table 1: Baseline characteristics of 262 study participants by HIV status				
Variables	**Total N = 262** **n (%)**	**PLHV, N = 145** **n (%)**	**HIV neg, N =117** **n (%)**	**p value**
Demographic Variables				
Age ≥55 years	**126 (48.1)**	**57(39.3)**	**69(59.0)**	**0.002**
Female sex	135(51.5)	81(55.9)	54(46.2)	0.12
Secondary education and above	107(40.8)	58(40.0)	49(41.9)	0.76
CVD history				
Prior stroke or MI	8(3.1)	6(4.1)	2(1.8)	0.30
Hypertension	**39(14.9)**	**15(10.3)**	**24(20.5)**	**0.02**
Hypertension treatment	**14(5.3)**	**5(3.4)**	**9(7.7)**	**0.03**
Diabetes treatment	2(0.01)	2(0.03)	0	
Lifestyle Factors				
Current smoker (<12 months)	13(5)	5(3.4)	8(6.8)	0.26
Ex-smoker	31(11.8)	16(11.0)	15(12.8)	0.65
Anthropometric factors				
Elevated BP	**64(24.4)**	**27(18.6)**	**37(33.3)**	**0.01**
Elevated BMI	88(33.6)	47(32.4)	41(35.0)	0.65
Abdominal obesity	65 (24.8)	33(22.8)	32(27.3)	0.39
Laboratory measurements*				
Elevated TC	56(22.8)	31(22.3)	25(23.4)	0.84
Elevated LDL-C	45(18.3)	22(15.9)	23(21.5)	0.22
Reduced HDL-C (males and females)	70(28.6)	33(23.9)	37(34.5)	0.06
Elevated TG	**23(9.4)**	**18(12.9)**	**5(4.7)**	**0.03**
Diabetes	6(2.4)	2(1.4)	4(3.7)	0.41
HIV related factors (median, IQR)				
Duration on ART (yrs)		9 (4.0-11.0)		
Current CD4 count(cells/mm^3)		489.0 (343.0-654.0)		
Nadir CD4 count (cells/mm^3)**		372 (215-546)		
VL suppressed***		139 (100)		
Undetectable VL		112(80.2)		

On ARV		145 (100)		
1st line regimen (non-PI)		121(83.4)		
2nd line regimen (PI)		24(16.6)		

* 16 missing values for laboratory measurements, 6 in PLHV group and 10 in HIV negative group. ** 8 missing observations for nadir CD4 count. *** 6 missing observations for viral load measurements

Abbreviations: HIV = human immunodeficiency virus, HTN = hypertension, CVD = cardiovascular disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein. TGs = triglycerides, MI = myocardial infarction. Viral load = VL, ARV = antiretroviral therapy, CD4 = cluster differentiation 4, PI = protease inhibitors, non-PI = non-protease inhibitors. IQR= interquartile range.

Definitions: BP ≥ 140mmHg or ≥ 90mmHg. Elevated BMI ($\geq$ 25kg/m^2). Abdominal obesity = waist circumference >88cm for women and >94cm for men. Elevated TC >200mg/dl. Elevated LDL-C >130mg/dl. Reduced HDL-C <50mg/dl for females and <40mg/dl for males. Elevated TG ≥150mg//dl. Diabetes = fasting glucose ≥126mg/dl. HIV related factors; Suppressed VL <1000copies/ml; Undetectable VL <50 copies/ml.

Table 2: Factors associated with differences in carotid intimal media thickness (CIMT) among all 262 study participants who underwent carotid ultrasound

Variables	Simple linear regression β coefficient (95% CI)	p value	Multivariable linear regression[1] β coefficient (95% CI)	p value
HIV positive status	-0.03(-0.07, -0.01)	**0.02**	-0.02(-0.05,0.01)	0.19
Demographic Variables				
≥ 55 years	0.05(0.01,0.07)	**0.004**	0.03(0.001,0.07)	**0.04**
Female sex	0.02(-0.01,0.05)	0.24		
Lifestyle factors				
Current smoker	-0.01-0.08,0.06)	0.76		
Ex-smoker	0.04(-0.01,0.08)	**0.12**	0.04(-0.01,0.08)	**0.15**
Secondary education or above	-0.01(-0.05,0.01)	0.26		
CVD history				
Hypertension	0.03(-0.01,0.07)	**0.15**	-0.01(-0.05,0.04)	0.83
Anthropometric factors				
Elevated BP or on treatment	0.05(0.01,0.08)	**0.01**	0.04(-0.005,0.07)	**0.09**
Elevated BMI	-0.01(-0.04,0.02)	0.40		
Abdominal obesity (females)	0.01(-0.03,0.05)	0.63		
Abdominal obesity (males)	-0.03(-0.10,0.037)	0.34		
Laboratory measurement				
Elevated TC	0.03(-0.01,0.07)	**0.10**	-0.0003(-0.06,0.06)	0.99
Elevated LDL-C	0.04(-0.01,0.07)	**0.06**	0.03(-0.02,0.07)	0.22
Reduced HDL- C (females)	-0.003(-0.05,0.04)	0.87		
Reduced HDL- C (males)	-0.03(-0.08,0.03)	0.38		
Elevated TG	-0.004(-0.06,0.05)	0.89		
Diabetes	0.12(0.02,0.22)	**0.02**	0.11(0.01, 0.21)	**0.02**

Abbreviations: HIV = human immunodeficiency virus, HTN = hypertension, CVD = cardiovascular disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein. TGs = triglycerides, MI = myocardial infarction. ART = antiretroviral therapy, CD4 = cluster differentiation 4, PI = protease inhibitors, Non PI = non-protease inhibitors.

Definitions: BP ≥ 140mmHg or ≥ 90mmHg. Elevated BMI ($\geq 25 kg/m^2$), Abdominal obesity = waist circumference >88cm for women and >94cm for men. Elevated TC >200mg/dl. Elevated LDL-C >130mg/dl. Reduced HDL-C <50mg/dl for females and <40mg/dl for males. Elevated TG ≥150mg//dl, Diabetes = fasting glucose ≥126mg/dl.

1. Final multivariable linear regression model best fit = older age, elevated BP/on treatment, ex smoking status and diabetes only.

Table 3: Factors associated with differences in CIMT among 145 HIV positive and 117 HIV negative participants				
	PLHV[2]		HIV negative[3]	
	β coefficient (95%CI)	p value	β coefficient (95%CI)	p value
Demographic variables				
Age ≥ 55 years	0.01 (-0.02,0.05)	0.50	0.07 (0.02,0.12)**	**0.006**
Female sex	0.03(-0.006,0.07)	0.10	0.01(-0.04,0.06)	0.66
Lifestyle factors				
Current smoker	-0.02(-0.12,0.08)	0.65	-0.01(-0.11,0.09)	0.78
Ex-smoker	0.04(-0.02,0.09)	0.23	0.03(-0.04,0.11)	0.36
Secondary education	-0.02(-0.06,0.0.02)	0.26	-0.01(-0.06,0.04)	0.57
CVD history				
Hypertension	0.03(-0.03,0.09)	0.36	0.02(-0.04,0.09)	0.49
Anthropometric factors				
Elevated BP or on treatment	0.06(0.02,0.11)	0.003*	0.01(-0.04,0.07)	0.59
Elevated BMI	0.004(-0.04,0.04)	0.84	-0.03(-0.09,0.02)	0.16
Abdominal obesity (females)	0.01(-0.04,0.06)	0.81	0.01(-0.07,0.08)	0.87
Abdominal obesity (males)	-0.002(-0.09,0.09)	0.96	-0.06(-0.17,0.04)	0.23
Laboratory measurement				
Elevated TC	-0.01(-0.05,0.04)	0.72	0.08(0.02,0.14)**	**0.01**
Elevated LDL-C	0.01(-0.05,0.06)	0.81	0.07(0.005,0.13)	0.04
Reduced HDL-C(females)	-0.004(-0.05,0.04)	0.87	-0.04(-0.12,0.04)	0.28
Reduced HDL-C (males)	0.002(-0.08,0.08)	0.95	-0.06(-0.14,0.02)	0.16
Elevated TG	-0.02(-0.08,0.04)	0.52	0.08(-0.05,0.20)	0.21
Diabetes	0.01(-0.15,0.17)	0.90	0.17(0.03,0.31)**	**0.02**
HIV related factors				
Duration on ART (yrs)	0.0004 (-0.004,0.004)	0.86		
CD4 count (current)	0.005 (-0.04,0.05	0.79		
CD4 count (nadir)	-0.003(-0.04,0.03)	0.86		
Undetectable VL	-0.02(-0.06,0.02)	0.38		
ARV 2nd line regimen (PI)	0.003(-0.05,0.05)	0.88		

Abbreviations: HIV = human immunodeficiency virus, HTN = hypertension, CVD = cardiovascular disease, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL = low density lipoprotein, HDL = high density lipoprotein. TGs = triglycerides, MI = myocardial infarction. ART = antiretroviral therapy, CD4 = cluster differentiation 4, PI = protease inhibitors, Non PI = non-protease inhibitors. 95% CI = 95% confidence interval

Definitions: Elevated BP ≥ 140mmHg or ≥90mmHg. Elevated BMI (≥ 25kg/m^2), Abdominal obesity = waist circumference >88cm for women and >94cm for men. Elevated TC >200mg/dl. Elevated LDL-C >130mg/dl, Elevated TG ≥150mg//dl. Reduced HDL-C <50mg/dl for females and <40mg/dl for males. Diabetes = fasting glucose ≥126mg/dl. HIV related factors; Suppressed VL <1000copies/ml; Undetectable VL <50 copies/ml.

2. Final multivariable linear regression model for PLHV: female sex; β coefficient = 0.03 ([95%CI: -0.004,0.07], p =0.08); elevated BP or on HTN treatment β coefficient = 0.07 ([95%CI: 0.02,0.11], p = **0.002**)*.

3. Final multivariable linear regression model: older age; β coefficient = 0.07 ([95% CI: 0.01,0.12], **p =0.01)**;** elevated BP or on HTN treatment;β coefficient = -0.04 ([95%CI; -0.09,0.15], p = 0.14); high TC; β coefficient = 0.09 ([95%CI: 0.03],0.14, **p = 0.01**)**; diabetes; β coefficient = 0.21([95% CI: 0.08,0.34], **p = 0.002**)**.