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ORIGINAL RESEARCH

Treated HIV Infection and Progression of Carotid Atherosclerosis in Rural Uganda: A Prospective Observational Cohort Study

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BACKGROUND: Although ≈70% of the world's population of people living with HIV reside in sub-Saharan Africa, there are minimal prospective data on the contributions of HIV infection to atherosclerosis in the region.

METHODS AND RESULTS: We conducted a prospective observational cohort study of people living with HIV on antiretroviral therapy >40 years of age in rural Uganda, along with population-based comparators not infected with HIV. We collected data on cardiovascular disease risk factors and carotid ultrasound measurements annually. We fitted linear mixed effects models, adjusted for cardiovascular disease risk factors, to estimate the association between HIV serostatus and progression of carotid intima media thickness (cIMT). We enrolled 155 people living with HIV and 154 individuals not infected with HIV and collected cIMT images at 1045 visits during a median of 4 annual visits per participant (interquartile range 3–4, range 1–5). Age (median 50.9 years) and sex (49% female) were similar by HIV serostatus. At enrollment, there was no difference in mean cIMT by HIV serostatus (0.665 versus 0.680 mm, P=0.15). In multivariable models, increasing age, blood pressure, and non–high-density lipoprotein cholesterol were associated with greater cIMT (P<0.05), however change in cIMT per year was also no different by HIV serostatus (0.004 mm/year for HIV negative [95% CI, 0.001–0.007 mm], 0.006 mm/year for people living with HIV [95% CI, 0.003–0.008 mm], HIV×time interaction P=0.25).

CONCLUSIONS: In rural Uganda, treated HIV infection was not associated with faster cIMT progression. These results do not support classification of treated HIV infection as a risk factor for subclinical atherosclerosis progression in rural sub-Saharan Africa.

REGISTRATION: URL: https://www.ClinicalTrials.gov; Unique identifier: NCT02445079.

Key Words: antiretroviral therapy ■ atherosclerosis ■ cardiovascular disease risk ■ carotid intima media thickness ■ HIV infection ■ Uganda

In the United States and Europe, HIV infection has been associated with increased rates of preclinical atherosclerosis, cardiovascular events, and cardiovascular death.[1–6] Whereas a portion of the increased risk among people living with HIV (PLWH) is ascribed to a higher prevalence of traditional cardiovascular disease (CVD) risk profiles, the increased risk persists after adjusting for these factors.[7] Consequently, CVD

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CLINICAL PERSPECTIVE

What Is New?

- In one of the first cohort studies in sub-Saharan Africa to include the collection of longitudinal data on carotid intima thickness, we found no difference in the presence or progression of carotid atherosclerosis over time between people with and without HIV.

What Are the Clinical Implications?

- Our data reinforce the need to promote local risk factor and outcome data collection to better elucidate the risk factors and public health response to cardiovascular disease among people living with HIV in sub-Saharan Africa.

Nonstandard Abbreviations and Acronyms

cIMT	carotid intima media thickness
NNRTI	nonnucleoside transcriptase inhibitor
PLWH	people living with HIV
UGANDAC	Ugandan Non-communicable Diseases and Aging Cohort Study

risk calculators appear to underestimate event risk in this population.[8] Although the field awaits the results of a large multinational study to assess the benefit of empiric statin therapy for the prevention of CVD events among PLWH with low to moderate risk,[9] the American College of Cardiology now considers HIV infection as a CVD risk enhancer.[10,11]

However, extrapolation of these data to HIV-endemic settings has been challenged by the lack of similarly supportive prospective data on relationships between HIV infection and CVD in such settings.[12] Although modeling studies suggest that a high burden of CVD is attributable to HIV in sub-Saharan Africa, these estimates presume that relationships between HIV and CVD risk in the global north are generalizable to the global south.[13] To date, few primary studies from sub-Saharan Africa have estimated associations between HIV and CVD risk. The majority of such studies have focused on risk factor prevalence, have assessed CVD risk before antiretroviral therapy (ART) suppression, have lacked HIV-uninfected comparator groups, and/or have been primarily cross-sectional in nature (particularly in the case of studies of atherosclerosis).[14–26]

Studies among appropriately matched people with and without HIV infection and monitored over time are needed to better advise CVD guidelines for PLWH in sub-Saharan Africa. To address this gap in the literature, we enrolled individuals with treated HIV infection from an ambulatory clinic in Uganda and sex-matched and age-matched comparators not infected with HIV from the clinic catchment area into a longitudinal prospective cohort study. Participants were followed annually for a median of 4 years to measure the progression of carotid atherosclerosis. Our overarching aim was to determine the contribution of treated HIV infection to preclinical atherosclerosis progression in rural sub-Saharan Africa. We hypothesized that, after adjustment for CVD risk factors, HIV serostatus would confer increased risk of carotid atherosclerosis progression over time.

METHODS

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Study Setting and Participants

The UGANDAC (Ugandan Non-communicable Diseases and Aging Cohort Study) was a longitudinal prospective cohort study that enrolled PLWH taking ART and HIV-uninfected, population-based comparators (NCT02445079). We have reported full details of the study design previoulsy.[21,27,28] We recruited PLWH age >40 years and on ART for a minimum of 3 years from the HIV clinic at the Mbarara Regional Referral Hospital Immune Suppression Syndrome Clinic. The HIV clinic serves a catchment area that includes the periurban Mbarara area and a large expanse of rural subdistricts in the region. After recruitment of PLWH, we recruited sex-matched and age-matched (by quartile of the PLWH population) comparators in a 1:1 ratio from the clinic catchment area using census data from a population-based partner study.[29] We conducted 2 waves of enrollment between December 2013 and December 2014 and between July 2015 and June 2016.

Study Procedures

Study participants were seen once annually for collection of measures until study completion in May 2018. Before each encounter, individuals not infected with HIV underwent confirmatory HIV testing following Ugandan Ministry of Health HIV Testing Guidelines.[30] At each visit, research nurses collected CVD risk factor data including smoking history, blood pressure measurements (Omron Healthcare Inc., Bannockburn, IL), hemoglobin A1c testing (Siemens Vantage, Siemens Healthcare Diagnostics, Tarrytown, NY), and blood samples for lipids and

inflammatory markers, which were cryopreserved at −80°C and later tested at the Laboratory for Clinical Biochemistry Research at the University of Vermont, as previously described.[28] CD4 count and viral load data were abstracted from the HIV clinic database.

Carotid Ultrasound Measurement and Interpretation

Two study staff members (J.H.K. and P.B.) were trained in carotid ultrasonography through the University of Wisconsin Carotid Intima Media Thickness Course and conducted all ultrasonography procedures.[31] Ultrasound images were collected using a Sonosite M-Turbo machine (Sonosite, Bothell, WA). We used a standardized imaging protocol to collect bilateral carotid artery images from the anterior, lateral, and posterior positions.[32] Full interpretation and quality control methods for image interpretation have been described previously.[21] In brief, we used a semiautomated edge-detection software platform (SonoCalc, Version 5.0, Sonosite) to measure 1-cm segments of the distal wall of the common carotid artery just proximal to the bulb, resulting in up to 6 carotid intima media thickness (cIMT) measures per participant per visit. All measurements were confirmed by a single reader (I.Y.) and reviewed for quality control by the study board-certified cardiologist (L.C.H.). Images of poor quality and those that were not captured at the same anatomical position required to measure the similar segment of the common carotid artery as other years in the study were discarded from the analysis.

Statistical Analysis

We first summarized the median observation time, compared reasons for dropout, and summed the proportion of high-quality cIMT images (both overall and by HIV serostatus). To assess for a possible bias attributed to loss from observation, we also compared sociodemographic and clinical factors between participants who completed ≤2 versus ≥3 study vistis. We then compared sociodemographic and CVD factor risk data, including Framingham risk score,[33] by HIV serostatus. We used mixed effects regression models to test the hypothesis that HIV infection was associated with the magnitude and trends over time of preclinical carotid atherosclerosis. Our primary outcome of interest was annual mean cIMT, estimated as the average value of all cIMT measures at each study visit. Our primary exposures of interest were HIV serostatus and years of observation. We fitted linear mixed effects models with time-updated mean cIMT as the outcome variable, a random effect for individual, HIV serostatus, time (years of observation), an HIV-by-time product term, and the following potential confounder variables (enrollment value carried forward, unless otherwise indicated): age, sex, mean systolic blood pressure, mean diastolic blood pressure, glycated hemoglobin A1c, smoking status (never, former, current), body mass index (categorized as <18.5, 18.5–25, 25–30, >30 kg/m^2), total cholesterol (per mg/dL), high-density lipoprotein (HDL; per mg/dL), non-HDL cholesterol (per mg/dL), creatinine (per mg/dL), albumin (per g/dL), log-transformed hs-CRP (high-sensitivity C-reactive protein; per mg/L), log-transformed soluble CD14 (per ng/mL), log-transformed soluble CD163 (per ng/mL), and log-transformed interleukin-6 (per pg/mL).

We fitted the following 4 sets of models: (1) single variable models including each covariate only; (2) multivariable models that included each covariate and adjusted for age and study observation time; (3) a multivariable model including all covariates, aside from biomarkers of inflammation, that reached statistical significance (as indicated by a P value of <0.25) for an association with mean cIMT in the age and observation time-adjusted models; and (4) a final multivariable model similar to model 3 with the addition of biomarkers of inflammation. For collinear variables achieving significance in minimally adjusted models (eg, total cholesterol and non-HDL cholesterol), we selected the variable with the greatest z score for incorporation into the multivariable model. The multivariable models included terms for HIV serostatus (to estimate the contribution of HIV to mean cIMT at enrollment), observation time at each visit (to estimate the change in mean cIMT over time in HIV-negative individuals), and a product term for HIV by observation time (to estimate the difference in change in mean cIMT over time between PLWH and comparators not infected with HIV).

Finally, we repeated the aforementioned process but restricted the analytic sample to PLWH and included HIV-specific explanatory variables, including CD4 count nadir (cells/μL), CD4 count at enrollment (cells/μL), time-updated CD4 count (cells/μL), viral suppression at enrollment (defined as below the limit of the assay used, which ranged from 40 to 550 copies/mL), time-updated viral suppression, and the use of a protease inhibitor versus a NNRTI (nonnucleoside transcriptase inhibitor)–based regimen.

Ethical Considerations

The study protocol was reviewed and approved by human subjects research review committees at Mbarara University of Science and Technology, Mass General Brigham, and the Ugandan National Council of Science and Technology. All participants gave signed informed consent or, for those unable to write, provided a thumbprint in the presence of a witness. Data requests from researchers with human subjects

confidentiality training may be sent to Mark Siedner at msiedner@mgh.harvard.edu.

RESULTS

A total of 309 individuals, including 155 (50%) PLWH, were enrolled between December 2013 and May 2016. All enrolled participants contributed at least 1 cIMT measurement to the analysis. Valid cIMT measurements were collected at 1045 of 1108 (94%) study visits during a median of 4 annual visits (interquartile range [IQR], 3–4; range, 1–5) and over a median of 3.0 years of observation time (IQR, 2.0–3.2; range, 0–4.3 years). Data from 1036 of these 1045 visits (99%) had complete covariate data and were included in multivariable models. The proportion of visits with a valid cIMT measurement was similar among participants not infected with HIV (485/523 [93%]) and among PLWH (560/585 [96%]). The number of visits per participant is summarized in Table S1 and was determined largely by the duration of time between enrollment and study closure. Demographic and clinical characteristics for participants completing <2 versus ≥3 cIMT visits are presented in Table S2. The 2 groups were similar, save a moderately lower proportion of women who completed ≥3 visits.

Of the 309 enrolled participants, 278 (90%) were retained until study closure. Of the other 31 individuals, 12 (38.9%) were PLWH, and the reasons for dropout were the following: 14 (4.5%) disenrolled, 9 (2.9%) were deceased, 6 (1.9%) were lost to follow-up, and 2 (0.7%) individuals not infected with HIV were disenrolled after an HIV seroconversion.

By design, participant sex (48.9% female) and median age at enrollment (50.9 years; IQR, 47.8–55.3) were similar by HIV serostatus (Table 1). Compared with individuals not infected with HIV, PLWH had lower systolic blood pressure (112.5 mm Hg versus 117.8 mm Hg; P=0.01) and lower diastolic blood pressure (69.0 mm Hg versus 77.0 mm Hg; P<0.001), and fewer were ever smokers (P<0.001). This combination of features led to a lower 10-year Framingham risk score among PLWH compared with the participants not infected with HIV (4.5% versus 6.1%; P=0.02). A similar proportion of participants had a reported history of hypertension in both groups (11.6% versus 13.6%; P=0.59), yet among those with such a history, PLWH were significantly more likely to report taking antihypertension therapy (66.7% versus 28.6%; P=0.02).

Compared with comparators not infected with HIV, PLWH had higher mean levels of hs-CRP and soluble CD14 at enrollment (P<0.001). The majority of PLWH (142/155, 92%) were taking an NNRTI-based regimen at enrollment. The median nadir CD4 count was 118 cells/μL (IQR, 74–183), but most had attained immune reconstitution with a median CD4 count by study enrollment (median, 433 cells/μL; IQR, 335–559), and most (133/155, 85.8%) had a viral load less than the limit of detection at enrollment. The majority remained virally suppressed throughout the observation period (113/155, 72.9%).

Unadjusted mean cIMT at enrollment was 0.665 mm among PLWH and 0.680 mm among participants not infected with HIV (difference, 0.017 mm; 95% CI, –0.006 to 0.041 mm; P=0.15). In single-variable, mixed effects regression models, multiple CVD risk factors, including older age, female sex, current smoking, and higher measures of systolic and diastolic blood pressure, hemoglobin A1c, body mass index, total and non-HDL cholesterol, and hs-CRP, were all associated with mean cIMT (Table 2).

In unadjusted models, mean cIMT increased by 0.005 mm/year of observation (95% CI, 0.003–0.007 mm/year) and was no different by HIV serostatus (HIV negative 0.004 mm/year [95% CI, 0.001–0.007 mm/year] versus PLWH 0.006 mm/year [95% CI, 0.003–0.008 mm/year], HIV-by-time interaction; P=0.32). In multivariable models adjusted for CVD risk factors, HIV serostatus was associated with neither mean cIMT at enrollment (mean difference, –0.014 mm; 95% CI, 0.034–0.006 mm; P=0.17) nor with progression of mean cIMT over time (difference, 0.002 mm/year; 95% CI, –0.002 to 0.006 mm/year, HIV-by-time interaction; P=0.25; Figure). Addition of inflammatory markers to the model did not have meaningful effects on associations between HIV and cIMT at enrollment or progression over time (Table 2).

In models restricted to PLWH, we found that age, systolic blood pressure, non-HDL cholesterol, hs-CRP, and years of observation were associated with cIMT (Table 3). In models adjusted for time-updated CD4 count and viral load, we found that use of protease inhibitor–based ART at enrollment was associated with increased cIMT compared with use of NNRTI-based ART (0.047 mm; 95% CI, 0.010–0.084 mm), but that time-updated CD4 count and HIV-1 RNA viral suppression were not.

DISCUSSION

In a prospective observational HIV cohort study in rural Uganda with >1000 annual study visits over a median of 4 visits per participants, we found no evidence for an increased prevalence or progression of preclinical atherosclerosis among individuals with treated HIV infection compared with comparators not infected with HIV in rural Uganda. Our results are generally consistent with other data from sub-Saharan Africa, which, unlike many studies from

Table 1. Participant Characteristics at Enrollment

Characteristic	Total Cohort (n=309)	HIV– (n=154)	PLWH (n=155)	*P* Value*
Age, y	50.9 (47.8 to 55.3)	51.0 (48.1 to 55.7)	50.8 (47.3 to 54.9)	0.42
Female sex	151 (48.9)	77 (50.0)	74 (47.7)	0.69
Mean systolic BP, mm Hg	114.5 (105.5 to 126.5)	117.8 (108 to 131.5)	112.5 (100.0 to 120.0)	0.01
Mean diastolic BP, mm Hg	73.0 (66.0 to 81.5)	77.0 (68.5 to 84.0)	69.0 (63.5 to 79.0)	<0.001
HbA1c, %	5.3 (5.0 to 5.7)	5.5 (5.2 to 5.9)	5.2 (5 to 5.6)	0.26
Smoking category				<0.001
Never	163 (52.8)	72 (46.8)	91 (58.7)	
Former	105 (34.0)	50 (32.5)	55 (35.5)	
Current	41 (13.3)	32 (20.8)	9 (5.8)	
BMI, kg/m^2	21.8 (19.6 to 25.2)	21.6 (19.1 to 24.9)	22.0 (19.9 to 25.2)	0.26
BMI category, kg/m^2				0.04
18–25	197 (63.8)	94 (61.0)	103 (66.5)	
<18	32 (10.4)	23 (14.9)	9 (5.8)	
25–30	51 (16.5)	21 (13.6)	30 (19.4)	
>30	29 (9.4)	16 (10.4)	13 (8.4)	
Total cholesterol, mg/dL	160 (136 to 182)	161 (139 to 181)	160 (131 to 183)	1.0
HDL cholesterol, mg/dL	45 (36 to 53)	45 (37 to 52)	44 (36 to 55)	0.49
Non-HDL cholesterol, mg/dL	108 (91 to 136)	108 (92 to 136)	108 (91 to 139)	0.71
Creatinine, mg/dL	0.77 (0.70 to 0.84)	0.77 (0.71 to 0.84)	0.76 (0.69 to 0.84)	0.57
Albumin, g/dL	4.3 (4.1 to 4.5)	4.3 (4.1 to 4.5)	4.3 (4 to 4.5)	0.75
Framingham 10-y risk, %	5.2 (2.9 to 8.9)	6.1 (3.1 to 9.4)	4.5 (2.7 to 7.8)	0.02
Reported history of hypertension, %	39 (12.6)	21 (13.6)	18 (11.6)	0.59
Current use of antihypertensive therapy, %	18 (46.1)	6 (28.6)	12 (66.7)	0.02
Log10 hs-CRP, mg/L	−0.10 (−0.40 to 0.38)	−0.22 (−0.64 to −0.16)	0.11 (−0.30 to 0.50)	<0.001
Log10 soluble CD14, ng/mL	3.12 (3.03 to 3.22)	3.08 (3.01 to 3.16)	3.17 (3.08 to 3.25)	<0.001
Log10 soluble CD163, ng/mL	2.69 (2.56 to 2.80)	2.70 (2.56 to 2.82)	2.68 (2.56 to 2.79)	0.16
Log10 IL-6, pg/mL	−0.40 (−0.53 to −0.22)	−0.40 (−0.52 to −0.27)	−0.40 (−0.53 to −0.18)	0.53
Log10 FABP-2, pg/mL	3.22 (3.07 to 3.37)	3.20 (3.05 to 3.32)	3.25 (3.08 to 3.42)	0.01
Nadir CD4 count, cells/μL	N/A	N/A	118 (74 to 183)	
Enrollment CD4 count, cells/μL	N/A	N/A	433 (335 to 559)	
Virologic suppression at enrollment	N/A	N/A	133 (85.8)	
Sustained virologic suppression during observation	N/A	N/A	113 (72.9)	
cIMT study visits completed	3 (4 to 4)	3 (2 to 4)	4 (3 to 4)	0.002

Data are provided as number (percentage) or median (interquartile range). BMI indicates body mass index; BP, blood pressure; cIMT, carotid intima media thickness; FABP-2, fatty acid binding protein-2; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; N/A, not applicable; and PLWH, people living with HIV.

* *P* values represent comparisons of summary measures between people living with HIV and HIV-uninfected individuals using rank-sum testing for nonnormally distributed continuous variables, *t* tests for normally distributed continuous variables, and χ^2 testing for categorical variables.

the global north, have demonstrated null or inverse associations between HIV infection and preclinical atherosclerotic burden.[34–36] In 1 important exception, a large study from South Africa (n=1927) detected higher mean cIMT among older PLWH on ART compared with comparators not infected with HIV and PLWH not on ART.[37] Our study builds on prior work with long-term prospective observation to measure progression of disease over time. Although additional longitudinal data from sub-Saharan Africa that capture CVD events will be required to conclusively elucidate these relationships, our results do not provide evidence for an increased risk of atherosclerosis among PLWH on ART treatment in the region.

Overall, we found a low rate of progression of carotid atherosclerosis in this Ugandan subpopulation

Table 2. Mixed Effects Linear Regression Models for Correlates of Carotid Intima Thickness Over 4 Years of Observation in Rural Uganda

Characteristic	Unadjusted Models		Age-Adjusted and Year-Adjusted Models		Adjusted Model Without Inflammatory Biomarkers		Fully Adjusted Model Including Inflammatory Biomarkers	
	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Age, per y	0.007 (0.006 to 0.008)	<0.001	N/A		0.007 (0.005 to 0.008)	<0.001	0.006 (0.005 to 0.008)	<0.001
Female sex	0.020 (0.001 to 0.039)	0.04	0.022 (0.005 to 0.039)	0.01	0.009 (–0.009 to 0.028)	0.31	0.006 (–0.013 to 0.025)	0.54
Mean systolic BP, mm Hg	0.002 (0.001 to 0.002)	<0.001	0.001 (0.000 to 0.002)	<0.001	…	…	…	…
Mean diastolic BP, mm Hg	0.002 (0.001 to 0.003)	<0.001	0.002 (0.001 to 0.002)	<0.001	0.001 (0.000 to 0.002)	0.05	0.001 (0.000 to 0.002)	0.07
HbA1c, %	0.019 (0.008 to 0.030)	0.001	0.018 (0.008 to 0.027)	<0.001	0.010 (0.000 to 0.019)	0.06	0.009 (–0.001 to 0.018)	0.09
Smoking category								
Never	Reference	…	Reference	…	Reference	…	Reference	…
Former	0.010 (–0.014 to 0.034)	0.42	–0.006 (–0.027 to 0.015)	0.57	0.002 (–0.019 to 0.023)	0.83	–0.002 (–0.023 to 0.019)	0.87
Current	–0.039 (–0.073 to –0.006)	0.02	–0.045 (–0.074 to –0.016)	0.002	–0.028 (–0.060 to 0.003)	0.08	–0.037 (–0.070 to –0.003)	0.03
BMI category, kg/m^2								
18–25	Reference	…	Reference	…	Reference	…	Reference	…
<18	0.009 (–0.027 to 0.046)	0.62	–0.011 (–0.043 to 0.021)	0.49	0.001 (–0.030 to 0.033)	0.94	0.001 (–0.032 to 0.034)	0.94
25–30	0.038 (0.008 to 0.068)	0.01	0.028 (0.002 to 0.054)	0.03	0.005 (–0.022 to 0.032)	0.74	–0.006 (–0.033 to 0.021)	0.67
>30	0.050 (0.012 to 0.088)	0.01	0.045 (0.012 to 0.078)	0.01	0.014 (–0.020 to 0.049)	0.42	–0.004 (–0.040 to 0.032)	0.82
Total cholesterol, 10 mg/dL	0.007 (0.004 to 0.010)	<0.001	0.005 (0.001 to 0.007)	<0.001	…	…	…	…
HDL cholesterol, 10 mg/dL	0.003 (–0.005 to 0.011)	0.45	–0.000 (–0.007 to 0.007)	0.95	…	…	…	…
Non-HDL cholesterol, 10 mg/dL	0.007 (0.004 to 0.010)	<0.001	0.005 (0.003 to 0.008)	<0.001	0.003 (0.000 to 0.006)	0.03	0.004 (0.001 to 0.007)	0.02
Creatinine, mg/dL	–0.050 (–0.133 to 0.033)	0.24	–0.031 (–0.103 to 0.040)	0.39	…	…	…	…
Albumin, g/dL	–0.003 (–0.035 to 0.028)	0.85	–0.008 (–0.035 to 0.019)	0.55	…	…	…	…
Log10 hs-CRP, mg/L	0.036 (0.016 to 0.056)	<0.001	0.026 (0.008 to 0.044)	0.004	…	…	0.024 (0.003 to 0.046)	0.03
Log10 soluble CD14, ng/mL	–0.065 (–0.148 to 0.019)	0.13	–0.056 (–0.128 to 0.016)	0.13	…	…	–0.086 (–0.163 to –0.009)	0.03
Log 10 soluble CD163, ng/mL	0.051 (–0.010 to 0.112)	0.10	0.029 (–0.025 to 0.082)	0.29	…	…	…	…
Log10 IL-6, pg/mL	0.045 (0.007 to 0.082)	0.02	0.037 (0.004 to 0.069)	0.03	…	…	0.021 (–0.015 to 0.058)	0.26
FABP-2	0.000 (–0.045 to 0.045)	0.99	0.014 (–0.025 to 0.052)	0.48	…	…	…	…
Years of observation	0.005 (0.003 to 0.007)	<0.001	N/A		0.003 (0.001 to 0.007)	0.01	0.004 (0.001 to 0.007)	0.02
HIV serostatus								
HIV uninfected	Reference	…	Reference	…	Reference	…	Reference	…
People living with HIV	–0.016 (–0.038 to 0.006)	0.16	–0.012 (–0.031 to 0.007)	0.20	–0.014 (–0.034 to 0.006)	0.17	–0.015 (–0.037 to 0.006)	0.17
HIV serostatus × observation time interaction term	N/A		N/A		0.002 (–0.002 to 0.006)	0.25	0.002 (–0.002 to 0.006)	0.26

BMI indicates body mass index; BP, blood pressure; FABP-2, fatty acid binding protein-2; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; and N/A/, not applicable.

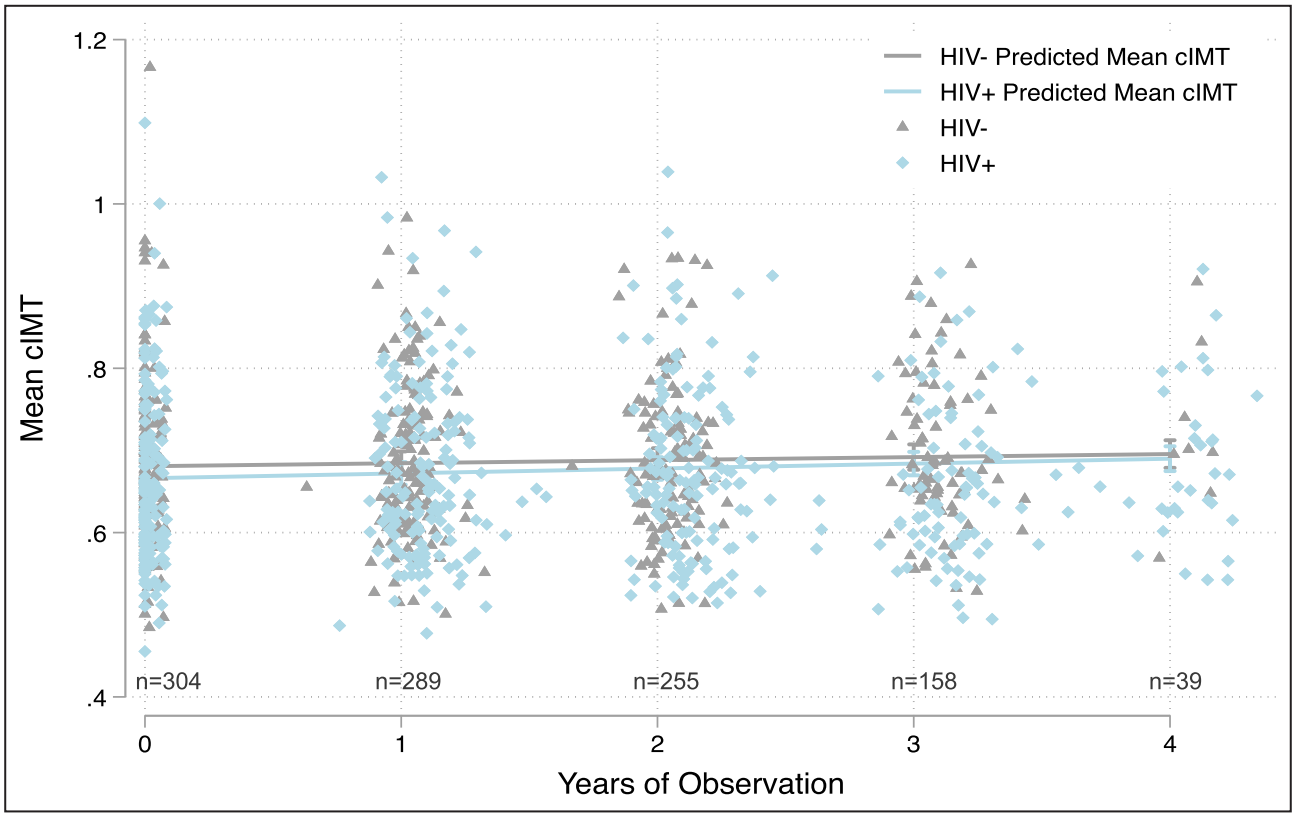

Figure. Scatter plot and model-adjusted estimates of mean cIMT by HIV serostatus over 4 years of observation in Uganda. cIMT indicates carotid intima media thickness. Estimates derived from a linear mixed effects model with cIMT as outcome and the following predictors of interest: sex, age, diastolic blood pressure, hemoglobin A1c, non-HDL cholesterol, and high-sensitivity C-reactive protein.

among the total cohort of PLWH and participants who were HIV negative (0.004 mm/year; 95% CI, 0.001–0.007). By contrast, numerous clinical cohort studies in the United States that include PLWH have tended to demonstrate substantially greater progression in common carotid atherosclerosis over time among both PLWH and comparators not infected with HIV, ranging from ≈0.006 to 0.050 mm/year.[38–41] Despite the low rates of progression demonstrated, we estimated a nonsignificantly greater rate of cIMT progression among PLWH compared with comparators not infected with HIV in Uganda (difference of 0.002 mm/year; 95% CI, −0.002 to 0.006 mm/year). Although this null finding might be attributable to limited power, the CIs we estimated at least partially exclude a clinically meaningful effect of HIV on atherosclerosis progression. For example, large observational cohorts and a recently published meta-analysis including >100 000 individuals have demonstrated that a threshold change in cIMT of 0.010 mm/year is required to predict a 10% increased rate of CVD events.[42,43] Nonetheless, the upper limit of our 95% CI (0.06 mm/year) does not fully exclude a clinical significant increased rate of change over time among PLWH.

Data from the global north have largely demonstrated relationships between HIV infection and atherosclerotic disease that appear to exceed risk afforded by traditional factors.[44–51] Notably, studies from the United States investigating the effect of HIV infection on cIMT progression are somewhat less robust, with reports variously demonstrating large and null effect sizes.[38,40,52,53] However on balance, the body of literature in this area has resulted in advocacy to include HIV as CVD risk enhancer in guidelines.[10,11] The effect of HIV infection on CVD risk tends to be greatest among people with lower CD4 counts and detectable viremia,[2,54,55] but whether such relationships apply to other populations is less well established. Similar to data from the global north, in this cohort from Uganda, we showed persistent elevations in markers of inflammation among ART-treated PLWH with immune reconstitution compared with individuals not infected with HIV[28] and that elevated hs-CRP was associated with preclinical atherosclerosis.[40,56] Also similar to prior data, we found preliminary evidence that use of older generation protease inhibitor–based ART (86% of those taking protease inhibitor–based therapy were on lopinavir/ritonavir) was associated with greater cIMT in models adjusted for age, viral load suppression,

Table 3. Mixed Effects Linear Regression Models for Correlates of Carotid Intima Thickness Restricted to People Living With HIV Over 4 Years of Observation in Rural Uganda

Characteristic	Unadjusted Models		Age-Adjusted and Year-Adjusted Models		Fully Adjusted Model	
	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Age, per y	0.006 (0.004 to 0.008)	<0.001	N/A	…	0.006 (0.004 to 0.008)	<0.001
Female sex	−0.006 (−0.034 to 0.022)	0.68	−0.001 (−0.026 to 0.025)	0.96		
Mean systolic BP, mm Hg	0.001 (0.000 to 0.002)	0.005	0.001 (0.000 to 0.002)	0.03	0.001 (0.000 to 0.001)	0.06
Mean diastolic BP, mm Hg	0.001 (0.000 to 0.002)	0.08	0.001 (0.000 to 0.002)	0.05		
HbA1c, %	0.017 (0.003 to 0.031)	0.02	0.017 (0.005 to 0.029)	0.007	0.008 (−0.005 to 0.022)	0.21
Smoking category						
Never	Reference	…	Reference	…	Reference	…
Former	−0.011 (−0.044 to 0.022)	0.53	−0.019 (−0.049 to 0.010)	0.20	−0.023 (−0.053 to 0.008)	0.15
Current	−0.041 (−0.108 to 0.027)	0.24	−0.043 (−0.103 to 0.017)	0.16	−0.034 (−0.094 to 0.026)	0.27
BMI category, kg/m^2						
18–25	Reference	…	Reference	…	Reference	…
<18	−0.013 (−0.080 to 0.055)	0.71	−0.043 (−0.104 to 0.018)	0.17	−0.042 (−0.101 to 0.017)	0.16
25–30	0.016 (−0.024 to 0.056)	0.44	0.000 (−0.035 to 0.036)	0.98	−0.031 (−0.069 to 0.007)	0.11
>30	0.037 (−0.020 to 0.094)	0.20	0.019 (−0.032 to 0.070)	0.46	−0.020 (−0.073 to 0.033)	0.45
Total cholesterol, 10 mg/dL	0.006 (0.002 to 0.010)	0.003	0.004 (0.001 to 0.008)	0.02		
HDL cholesterol, 10 mg/dL	0.005 (−0.007 to 0.017)	0.39	0.004 (−0.006 to 0.015)	0.44		
Non-HDL cholesterol, 10 mg/dL	0.006 (0.002 to 0.011)	0.01	0.005 (0.001 to 0.009)	0.02	0.004 (0.000 to 0.008)	0.04
Creatinine, mg/dL	−0.023 (−0.125 to 0.079)	0.66	0.000 (−0.091 to 0.092)	0.99		
Albumin, g/dL	−0.001 (−0.041 to 0.040)	0.98	−0.003 (−0.039 to 0.033)	0.87		
Log10 hs-CRP, mg/L	0.040 (0.012 to 0.069)	0.005	0.020 (−0.007 to 0.047)	0.14	0.025 (−0.002 to 0.051)	0.07
Log10 soluble CD14, ng/mL	−0.053 (−0.182 to 0.075)	0.42	−0.042 (−0.158 to 0.074)	0.48		
Log 10 soluble CD163, ng/mL	0.045 (−0.043 to 0.133)	0.32	0.037 (−0.043 to 0.116)	0.37		
Log10 IL-6, pg/mL	0.028 (−0.021 to 0.077)	0.27	0.021 (−0.023 to 0.065)	0.36		
Log10 FABP-2	0.014 (−0.049 to 0.077)	0.66	0.028 (−0.028 to 0.085)	0.33		
PI-based ART (vs NNRTI)	0.028 (−0.015 to 0.071)	0.20	0.042 (0.002 to 0.082)	0.04	0.047 (0.010 to 0.084)	0.05
CD4 count nadir, cells/μL	0.000 (0.000 to 0.000)	0.07	0.000 (0.000 to 0.000)	0.79		
CD4 count at enrollment, 100 cells/μL	0.000 (0.000 to 0.000)	0.30	0.000 (0.000 to 0.000)	0.69		
Time-updated CD4 count, 100 cells/μL	0.002 (−0.002 to 0.007)	0.30	−0.000 (−0.005 to 0.004)	0.89		
Viral load suppression at enrollment	0.032 (−0.012 to 0.077)	0.15	0.009 (−0.032 to 0.050)	0.44		
Time-updated viral load	0.014 (0.001 to 0.027)	0.03	0.010 (−0.003 to 0.022)	0.14	0.010 (−0.002 to 0.022)	0.12
Years of observation	0.006 (0.003 to 0.008)	<0.001	N/A	…	0.005 (0.003 to 0.008)	<0.001

ART indicates antiretroviral therapy; BMI, body mass index; BP, blood pressure; FABP-2, fatty acid binding protein-2; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin 6; N/A, not applicable; NNRTI, nonnucleoside reverse transcriptase inhibitor; and PI, protease inhibitor.

and CVD risk factors.[57–60] Thus, the pathophysiologic mechanisms by which HIV and its treatment putatively contribute to atherosclerotic CVD risk appear to apply to sub-Saharan African populations as well.[61]

Notably, unlike in the United States, where traditional CVD risk factors tend to be worse among PLWH in many cohorts,[7,62] we found an inverse relationship in our cohort, such that PLWH had improved profiles and lower Framingham risk scores than age and sex-matched uninfected comparators. Indeed, evidence is emerging across the sub-Saharan African region that, although PLWH in sub-Saharan Africa also have evidence of chronic immune activation despite suppressive ART,[28,63,64] they appear to have favorable traditional CVD risk profiles compared with people without HIV,[16,19,65,66] potentially attributed to the fact that the HIV care programs have become de facto and well-funded primary care platforms not typically

afforded to the general public.[67] We found some supporting evidence of this phenomenon in this cohort, with a greater proportion of PLWH with self-reported hypertension taking antihypertensives compared with individuals not infected with HIV with self-reported hypertension. Although the ultimate effect of these countervailing forces remains unknown, our data lend support to a hypothesis that relatively improved CVD risk profiles among PLWH might reduce the deleterious effect of chronic inflammation to preclinical atherosclerotic risk.

Our data reinforce the importance of improving primary healthcare delivery in sub-Saharan Africa to target CVD risk factor monitoring and control. High blood pressure, impaired glucose tolerance, high cholesterol, and in unadjusted models, higher body mass index predicted a greater degree of carotid atherosclerosis in our cohort. Whereas primary care guidelines for HIV care are robust and largely successful across sub-Saharan Africa, similar funding for and public health attention to CVD risk factor screening, awareness, and interventions in the general population has been comparatively scant in the region.[68–71]

This study was strengthened through prospective observation of individuals over multiple years and selection of community-dwelling, age-matched and sex-matched comparators not infected with HIV enrolled from the same geographic region as PLWH. The validity of our results is further supported by the fact that multiple traditional risk factors, including high blood pressure, elevated hemoglobin A1c, dyslipidemia, older age, and observation time correlated with greater cIMT.

As with all observational cohort studies, our results are susceptible to unmeasured and residual confounding. Although this is among the largest longitudinal cohorts involving PLWH with carotid ultrasonography in the region, our CIs, which extend to 0.06 mm/year difference in progression between PLWH and individuals not infected with HIV, allow for the possibility of a deleterious (or beneficial) impact of HIV on atherosclerosis. Moreover, our primary outcome of interest, cIMT, is a preclinical surrogate marker of atherosclerosis, which is a validated predictor of CVD events in the global north.[43,72,73] However, validation data are not available for sub-Saharan Africa. cIMT measurement is also susceptible to variability between technicians and readers. We attempted to mitigate these effects through standardized training of ultrasonographers, use of semiautomated detection software, and review of all images by a board-certified study cardiologist. Finally, our results should only be generalized to similar populations, which include PLWH enrolled in routine care who have largely achieved successful virologic suppression in resource-limited, periurban and rural locales in the region.

In summary, we found significant contributions of traditional CVD risk factors, but not of treated HIV infection, on carotid atherosclerosis over 4 years among older individuals in Uganda. We found that PLWH had increased biomarkers of inflammation but improved CVD risk profiles and suspect that these forces might offset each other. Future work in this area should consider the effect of HIV on CVD outcomes and explore broadening access to primary care of CVD disease within the general population.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S2

REFERENCES

1. Zanni MV, Schouten J, Grinspoon SK, Reiss P. Risk of coronary heart disease in patients with HIV infection. *Nat Rev Cardiol*. 2014;11:728–741. DOI: 10.1038/nrcardio.2014.167.
2. Siedner MJ. Start or smart? Timing of antiretroviral therapy initiation and cardiovascular risk for people with human immunodeficiency virus infection. *Open Forum Infect Dis*. 2016;3:ofw032. DOI: 10.1093/ofid/ofw032.

3. Hsue PY, Tawakol A. Inflammation and fibrosis in HIV. *Circ Cardiovasc Imaging*. 2016;9:e004427. DOI: 10.1161/CIRCIMAGING.116.004427.
4. Hanna DB, Lin J, Post WS, Hodis HN, Xue X, Anastos K, Cohen MH, Gange SJ, Haberlen SA, Heath SL, et al. Association of macrophage inflammation biomarkers with progression of subclinical carotid artery atherosclerosis in HIV-infected women and men. *J Infect Dis*. 2017;215:1352–1361. DOI: 10.1093/infdis/jix082.
5. McKibben RA, Margolick JB, Grinspoon S, Li X, Palella FJ, Kingsley LA, Witt MD, George RT, Jacobson LP, Budoff M, et al. Elevated levels of monocyte activation markers are associated with subclinical atherosclerosis in men with and those without HIV infection. *J Infect Dis*. 2015;211:1219–1228. DOI: 10.1093/infdis/jiu594.
6. Hsue PY, Hunt PW, Schnell A, Kalapus SC, Hoh R, Ganz P, Martin JN, Deeks SG. Role of viral replication, antiretroviral therapy, and immunodeficiency in HIV-associated atherosclerosis. *AIDS*. 2009;23:1059–1067. DOI: 10.1097/QAD.0b013e32832b514b.
7. Paisible A-L, Chang C-C, So-Armah KA, Butt AA, Leaf DA, Budoff M, Rimland D, Bedimo R, Goetz MB, Rodriguez-Barradas MC, et al. HIV infection, cardiovascular disease risk factor profile, and risk for acute myocardial infarction. *J Acquir Immune Defic Syndr*. 2015;68:209–216. DOI: 10.1097/QAI.0000000000000419.
8. Triant VA, Perez J, Regan S, Massaro JM, Meigs JB, Grinspoon SK, D'Agostino RB. Cardiovascular risk prediction functions underestimate risk in HIV infection. *Circulation*. 2018;137:2203–2214. DOI: 10.1161/CIRCULATIONAHA.117.028975.
9. Grinspoon SK, Fitch KV, Overton ET, Fichtenbaum CJ, Zanni MV, Aberg JA, Malvestutto C, Lu MT, Currier JS, Sponseller CA, et al. Rationale and design of the randomized trial to prevent vascular events in HIV (REPRIEVE). *Am Heart J*. 2019;212:23–35. DOI: 10.1016/j.ahj.2018.12.016.
10. Hsue PY, Waters DD. Time to recognize HIV infection as a major cardiovascular risk factor. *Circulation*. 2018;138:1113–1115. DOI: 10.1161/CIRCULATIONAHA.118.036211.
11. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, Grinspoon SK, Levin J, Longenecker CT, Post WS. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. *Circulation*. 2019;140:e98–e124. DOI: 10.1161/CIR.0000000000000695.
12. Feinstein MJ, Bogorodskaya M, Bloomfield GS, Vedanthan R, Siedner MJ, Kwan GF, Longenecker CT. Cardiovascular complications of HIV in endemic countries. *Curr Cardiol Rep*. 2016;18:113. DOI: 10.1007/s11886-016-0794-x.
13. Shah MR, Cook N, Wong R, Hsue P, Ridker P, Currier J, Shurin S. Stimulating high impact HIV-related cardiovascular research: recommendations from a multidisciplinary NHLBI Working Group on HIV-related heart, lung, and blood disease. *J Am Coll Cardiol*. 2015;65:738–744. DOI: 10.1016/j.jacc.2014.12.014.
14. Hyle EP, Mayosi BM, Middelkoop K, Mosepele M, Martey EB, Walensky RP, Bekker L-G, Triant VA. The association between HIV and atherosclerotic cardiovascular disease in sub-Saharan Africa: a systematic review. *BMC Public Health*. 2017;17:954. DOI: 10.1186/s12889-017-4940-1.
15. Abdallah A, Chang JL, O'Carroll CB, Musubire A, Chow FC, Wilson AL, Siedner MJ. Stroke in human immunodeficiency virus-infected individuals in sub-Saharan Africa (SSA): a systematic review. *J Stroke Cerebrovasc Dis*. 2018;27:1828–1836. DOI: 10.1016/j.jstrokecerebrovasdis.2018.02.016.
16. Feinstein MJ, Kim J-H, Bibangambah P, Sentongo R, Martin JN, Tsai AC, Bangsberg DR, Hemphill L, Triant VA, Boum Y II, et al. Ideal cardiovascular health and carotid atherosclerosis in a mixed cohort of HIV-infected and uninfected Ugandans. *AIDS Res Hum Retroviruses*. 2017;33:49–56. DOI: 10.1089/aid.2016.0104.
17. Muiru AN, Bibangambah P, Hemphill L, Sentongo R, Kim J-H, Triant VA, Bangsberg DR, Tsai AC, Martin JN, Haberer JE, et al. Distribution and performance of cardiovascular risk scores in a mixed population of HIV-infected and community-based HIV-uninfected individuals in Uganda. *J Acquir Immune Defic Syndr*. 2018;78:458–464. DOI: 10.1097/QAI.0000000000001696.
18. Muyanja D, Muzoora C, Muyingo A, Muyindike W, Siedner MJ. High prevalence of metabolic syndrome and cardiovascular disease risk among people with HIV on stable ART in southwestern Uganda. *AIDS Patient Care STDS*. 2016;30:4–10. DOI: 10.1089/apc.2015.0213.
19. Okello S, Asiimwe SB, Kanyesigye M, Muyindike WR, Boum Y II, Mwebesa BB, Haberer JE, Huang Y, Williams K, Burdo TH, et al. D-dimer levels and traditional risk factors are associated with incident hypertension among HIV-infected individuals initiating antiretroviral therapy in Uganda. *J Acquir Immune Defic Syndr*. 2016;73:396–402. DOI: 10.1097/QAI.0000000000001074.
20. Siedner MJ, Kim JH, Haberer JE, Martin JN, Boum Y II, Tsai AC, Hunt P, Bangsberg DR. HIV infection and vascular stiffness among older adults taking antiretroviral therapy in rural uganda. *8th International AIDS Society Conference on HIV Pathogenesis*. *19-22 July 2015*. Vancouver, Canada; 2015.
21. Siedner MJ, Kim J-H, Nakku RS, Bibangambah P, Hemphill L, Triant VA, Haberer JE, Martin JN, Mocello AR, Boum Y, et al. Persistent immune activation and carotid atherosclerosis in HIV-infected Ugandans receiving antiretroviral therapy. *J Infect Dis*. 2016;213:370–378. DOI: 10.1093/infdis/jiv450.
22. Alencherry B, Erem G, Mirembe G, Ssinabulya I, Yun C-H, Hung C-L, Siedner MJ, Bittencourt M, Kityo C, McComsey GA, et al. Coronary artery calcium, HIV and inflammation in uganda compared with the USA. *Open Heart*. 2019;6:e001046. DOI: 10.1136/openhrt-2019-001046.
23. Ssinabulya I, Kayima J, Longenecker C, Luwedde M, Semitala F, Kambugu A, Ameda F, Bugeza S, McComsey G, Freers J, et al. Subclinical atherosclerosis among HIV-infected adults attending HIV/AIDS care at two large ambulatory HIV clinics in Uganda. *PLoS One*. 2014;9:e89537. DOI: 10.1371/journal.pone.0089537.
24. Fourie C, van Rooyen J, Pieters M, Conradie K, Hoekstra T, Schutte A. Is HIV-1 infection associated with endothelial dysfunction in a population of African ancestry in South Africa? *Cardiovasc J Afr*. 2011;22:134–140. DOI: 10.5830/CVJA-2010-056.
25. Fourie CM, Schutte AE, Smith W, Kruger A, van Rooyen JM. Endothelial activation and cardiometabolic profiles of treated and never-treated HIV infected africans. *Atherosclerosis*. 2015;240:154–160. DOI: 10.1016/j.atherosclerosis.2015.03.015.
26. Botha S, Fourie CMT, van Rooyen JM, Kruger A, Schutte AE. Cardiometabolic changes in treated versus never treated HIV-infected black South Africans: the PURE study. *Heart Lung Circ*. 2014;23:119–126. DOI: 10.1016/j.hlc.2013.07.019.
27. Siedner MJ, Kim J-H, Nakku RS, Hemphill L, Triant VA, Haberer JE, Martin JN, Boum Y II, Kwon DS, Tsai AC, et al. HIV infection and arterial stiffness among older-adults taking antiretroviral therapy in rural Uganda. *AIDS*. 2016;30:667–670. DOI: 10.1097/QAD.0000000000000992.
28. Siedner MJ, Zanni M, Tracy RP, Kwon DS, Tsai AC, Kakuhire B, Hunt PW, Okello S. Increased systemic inflammation and gut permeability among women with treated HIV infection in rural Uganda. *J Infect Dis*. 2018;218:922–926. DOI: 10.1093/infdis/jiy244.
29. Takada S, Nyakato V, Nishi A, O'Malley AJ, Kakuhikire B, Perkins JM, Bangsberg DR, Christakis NA, Tsai AC. The social network context of HIV stigma: population-based, sociocentric network study in rural Uganda. *Soc Sci Med*. 2019;233:229–236. DOI: 10.1016/j.socscimed.2019.05.012.
30. Ugandan Ministry of Health. *National HIV Testing Services Policy and Implementation Guidelines*. 4th ed. October Kampala, Uganda: Ugandan Ministry of Health; 2016. Available at: http://library.health.go.ug/download/file/fid/2140. Accessed October 1, 2020.
31. Korcarz CE, Hirsch AT, Bruce C, DeCara JM, Mohler ER, Pogue B, Postley J, Tzou WS, Stein JH. Carotid intima-media thickness testing by non-sonographer clinicians: the office practice assessment of carotid atherosclerosis study. *J Am Soc Echocardiogr*. 2008;21:117–122. DOI: 10.1016/j.echo.2007.08.038.
32. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, Najjar SS, Rembold CM, Post WS; American Society of Echocardiography Carotid Intima-Media Thickness Task F. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr*. 2008;21:93–111; quiz 189–190. DOI: 10.1016/j.echo.2007.11.011.
33. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753. DOI: 10.1161/CIRCULATIONAHA.107.699579.
34. Nonterah EA, Boua PR, Klipstein-Grobusch K, Asiki G, Micklesfield LK, Agongo G, Ali SA, Mashinya F, Sorgho H, Nakanabo-Diallo S, et al. Classical cardiovascular risk factors and HIV are associated with carotid intima-media thickness in adults from Sub-Saharan Africa: findings

from H3Africa AWI-Gen study. *J Am Heart Assoc*. 2019;8:e011506. DOI: 10.1161/JAHA.118.011506.
35. Mosepele M, Hemphill LC, Moloi W, Moyo S, Nkele I, Makhema J, Bennett K, Triant VA, Lockman S. Pre-clinical carotid atherosclerosis and sCD163 among virally suppressed HIV patients in Botswana compared with uninfected controls. *PLoS One*. 2017;12:e0179994. DOI: 10.1371/journal.pone.0179994.
36. Vos AG, Hoeve K, Barth RE, Peper J, Moorhouse M, Crowther NJ, Venter WDF, Grobbee DE, Bots ML, Klipstein-Grobusch K. Cardiovascular disease risk in an urban African population: a cross-sectional analysis on the role of HIV and antiretroviral treatment. *Retrovirology*. 2019;16:37. DOI: 10.1186/s12977-019-0497-7.
37. Vos AG, Barth RE, Klipstein-Grobusch K, Tempelman HA, Devillé WLJ, Dodd C, Coutinho RA, Grobbee DE. Cardiovascular disease burden in rural Africa: does HIV and antiretroviral treatment play a role? *J Am Heart Assoc*. 2020;9:e013466. DOI: 10.1161/JAHA.119.013466.
38. Hsue PY, Scherzer R, Hunt PW, Schnell A, Bolger AF, Kalapus SC, Maka K, Martin JN, Ganz P, Deeks SG. Carotid intima-media thickness progression in HIV-infected adults occurs preferentially at the carotid bifurcation and is predicted by inflammation. *J Am Heart Assoc*. 2012;1:jah3-e000422. DOI: 10.1161/JAHA.111.000422.
39. Baker JV, Henry WK, Patel P, Bush TJ, Conley LJ, Mack WJ, Overton ET, Budoff M, Hammer J, Carpenter CC, et al. Progression of carotid intima-media thickness in a contemporary human immunodeficiency virus cohort. *Clin Infect Dis*. 2011;53:826–835. DOI: 10.1093/cid/cir497.
40. Hileman CO, Longenecker CT, Carman TL, McComsey GA. C-reactive protein predicts 96-week carotid intima media thickness progression in HIV-infected adults naive to antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2014;65:340–344. DOI: 10.1097/QAI.0000000000000063.
41. Currier JS, Kendall MA, Henry WK, Alston-Smith B, Torriani FJ, Tebas P, Li Y, Hodis HN. Progression of carotid artery intima-media thickening in HIV-infected and uninfected adults. *AIDS*. 2007;21:1137–1145. DOI: 10.1097/QAD.0b013e32811ebf79.
42. Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao LU, Liao X, Lonn E, Gerstein HC, Yusuf S, et al. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk. *Circulation*. 2020;142:621–642. DOI: 10.1161/CIRCULATIONAHA.120.046361.
43. Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, Azen SP. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med*. 1998;128:262–269. DOI: 10.7326/0003-4819-128-4-199802150-00002.
44. D'Ascenzo F, Cerrato E, Calcagno A, Grossomarra W, Ballocca F, Omedè P, Montefusco A, Veglia S, Barbero U, Gili S, et al. High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis. *Atherosclerosis*. 2015;240:197–204. DOI: 10.1016/j.atherosclerosis.2015.03.019.
45. Post WS, Budoff M, Kingsley L, Palella FJ Jr, Witt MD, Li X, George RT, Brown TT, Jacobson LP. Associations between HIV infection and subclinical coronary atherosclerosis. *Ann Intern Med*. 2014;160:458–467. DOI: 10.7326/M13-1754.
46. Zanni MV, Abbara S, Lo J, Wai B, Hark D, Marmarelis E, Grinspoon SK. Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2013;27:1263–1272. DOI: 10.1097/QAD.0b013e32835eca9b.
47. Freiberg MS, Chang C-C, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, Rimland D, Goetz MB, Butt AA, Rodriguez Barradas MC, et al. The risk of incident coronary heart disease among Veterans with and without HIV and hepatitis C. *Circ Cardiovasc Qual Outcomes*. 2011;4:425–432. DOI: 10.1161/CIRCOUTCOMES.110.957415.
48. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, Nasir K, Grinspoon SK. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2010;24:243–253. DOI: 10.1097/QAD.0b013e328333ea9e.
49. Fitch KV, Lo J, Abbara S, Ghoshhajra B, Shturman L, Soni A, Sacks R, Wei J, Grinspoon S. Increased coronary artery calcium score and noncalcified plaque among HIV-infected men: relationship to metabolic syndrome and cardiac risk parameters. *J Acquir Immune Defic Syndr*. 2010;55:495–499. DOI: 10.1097/QAI.0b013e3181edab0b.
50. Kingsley LA, Cuervo-Rojas J, Munoz A, Palella FJ, Post W, Witt MD, Budoff M, Kuller L. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. *AIDS*. 2008;22:1589. DOI: 10.1097/QAD.0b013e328306a6c5.
51. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, et al. Arterial inflammation in patients with HIV. *JAMA*. 2012;308:379–386. DOI: 10.1001/jama.2012.6698.
52. Hanna DB, Post WS, Deal JA, Hodis HN, Jacobson LP, Mack WJ, Anastos K, Gange SJ, Landay AL, Lazar JM, et al. HIV infection is associated with progression of subclinical carotid atherosclerosis. *Clin Infect Dis*. 2015;61:640–650. DOI: 10.1093/cid/civ325.
53. Hileman CO, Carman TL, Longenecker CT, Labbato DE, Storer NJ, White CA, McComsey GA. Rate and predictors of carotid artery intima media thickness progression in antiretroviral-naive HIV-infected and uninfected adults: a 48-week matched prospective cohort study. *Antivir Ther*. 2013;18:921–929. DOI: 10.3851/IMP2651.
54. Klein DB, Leyden WA, Xu L, Chao CR, Horberg MA, Towner WJ, Hurley LB, Marcus JL, Quesenberry CP Jr, Silverberg MJ. Declining relative risk for myocardial infarction among HIV-positive compared with HIV-negative individuals with access to care. *Clin Infect Dis*. 2015;60:1278–1280. DOI: 10.1093/cid/civ014.
55. INSIGHT START Study Group, Lundgren JD, Babiker AG, Gordin F, Emery S, Grund B, Sharma S, Avihingsanon A, Cooper DA, Fatkenheuer G, Llibre JM, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373:795–807. DOI: 10.1056/NEJMoa1506816.
56. Triant VA, Meigs JB, Grinspoon SK. Association of c-reactive protein and HIV infection with acute myocardial infarction. *J Acquir Immune Defic Syndr*. 2009;51:268–273. DOI: 10.1097/QAI.0b013e3181a9992c.
57. Schillaci G, De Socio GV, Pirro M, Savarese G, Mannarino MR, Baldelli F, Stagni G, Mannarino E. Impact of treatment with protease inhibitors on aortic stiffness in adult patients with human immunodeficiency virus infection. *Arterioscler Thromb Vasc Biol*. 2005;25:2381–2385. DOI: 10.1161/01.ATV.0000183744.38509.de.
58. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D; Clinical Epidemiology Group from the French Hospital D. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS*. 2003;17:2479–2486. DOI: 10.1097/00002030-200311210-00010.
59. Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, Greenberg AE, Janssen RS; Investigators HIVOS. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet*. 2002;360:1747–1748. DOI: 10.1016/S0140-6736(02)11672-2.
60. DAD Study Group; Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, Thiebaut R, De Wit S, Kirk O, Fontas E, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007;356:1723–1735. DOI: 10.1056/NEJMoa062744.
61. Hunt PW, Lee SA, Siedner MJ. Immunologic biomarkers, morbidity, and mortality in treated HIV infection. *J Infect Dis*. 2016;214(suppl 2):S44–S50. DOI: 10.1093/infdis/jiw275.
62. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92:2506–2512. DOI: 10.1210/jc.2006-2190.
63. Bipath P, Levay PF, Viljoen M. The kynurenine pathway activities in a sub-saharan HIV/AIDS population. *BMC Infect Dis*. 2015;15:346. DOI: 10.1186/s12879-015-1087-5.
64. Cassol E, Malfeld S, Mahasha P, van der Merwe S, Cassol S, Seebregts C, Alfano M, Poli G, Rossouw T. Persistent microbial translocation and immune activation in HIV-1-infected South Africans receiving combination antiretroviral therapy. *J Infect Dis*. 2010;202:723–733. DOI: 10.1086/655229.
65. Manne-Goehler J, Montana L, Gómez-Olivé FX, Rohr J, Harling G, Wagner RG, Wade A, Kabudula CW, Geldsetzer P, Kahn K, et al. The ART advantage: health care utilization for diabetes and hypertension in rural South Africa. *J Acquir Immune Defic Syndr*. 2017;75:561–567. DOI: 10.1097/QAI.0000000000001445.
66. Mitton JA, North CM, Muyanja D, Okello S, Vorechovska D, Kakuhikire B, Tsai AC, Siedner MJ. Smoking cessation after engagement in HIV care in rural Uganda. *AIDS Care*. 2018;30:1622–1629. DOI: 10.1080/09540121.2018.1484070.
67. Okello S, Amir A, Bloomfield GS, Kentoffio K, Lugobe HM, Reynolds Z, Magodoro IM, North CM, Okello E, Peck R, et al. Prevention of cardiovascular disease among people living with HIV in sub-Saharan Africa. *Prog Cardiovasc Dis*. 2020;63:149–159. DOI: 10.1016/j.pcad.2020.02.004.
68. Lee A, Boateng D, Wekesah F, Browne JL, Agyemang C, Agyei-Baffour P, Aikins A-G, Smit HA, Grobbee DE, Klipstein-Grobusch K. Knowledge

and awareness of and perception towards cardiovascular disease risk in sub-Saharan Africa: a systematic review. *PLoS One*. 2017;12:e0189264. DOI: 10.1371/journal.pone.0189264.
69. Irazola VE, Gutierrez L, Bloomfield G, Carrillo-Larco RM, Prabhakaran D, Gaziano T, Levitt NS, Miranda JJ, Ortiz AB, Steyn K, et al. Hypertension prevalence, awareness, treatment, and control in selected LMIC communities: results from the NHLBI/UHG Network of centers of excellence for chronic diseases. *Glob Heart*. 2016;11:47–59. DOI: 10.1016/j.gheart.2015.12.008.
70. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation*. 2016;134:441–450. DOI: 10.1161/CIRCULATIONAHA.115.018912.
71. Wollum A, Gabert R, McNellan CR, Daly JM, Reddy P, Bhatt P, Bryant M, Colombara DV, Naidoo P, Ngongo B, et al. Identifying gaps in the continuum of care for cardiovascular disease and diabetes in two communities in South Africa: baseline findings from the HealthRise project. *PLoS One*. 2018;13:e0192603. DOI: 10.1371/journal.pone.0192603.
72. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam study. *Circulation*. 1997;96:1432–1437. DOI: 10.1161/01.CIR.96.5.1432.
73. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999;340:14–22. DOI: 10.1056/NEJM199901073400103.

SUPPLEMENTAL MATERIAL

Table S1. Total visits with a cIMT measurement by study group.

Total cIMT Visits	Total Cohort	HIV- (n=154)	PLWH (n=155)
1, n (%)	21 (7%)	17 (11%)	4 (3%)
2, n (%)	35 (11%)	25 (16%)	10 6%)
3, n (%)	97 (31%)	38 (25%)	59 (38%)
4, n (%)	119 (39%)	66 (43%)	53 (34%)
5, n (%)	37 (12%)	8 (5%)	29 (19%)

PLWH: People living with HIV

Table S2. Participant demographic and clinical characteristics at enrollment by completion of three or more study visits.

Characteristics	Completed two or fewer cIMT Visits (n=56)	Completed three or more cIMT visits (n=253)	*P*-value
Age, median (IQR)	51 (49, 56)	51 (47, 55)	0.29
Female sex, n (%)	34 (61%)	117 (46%)	0.05
Systolic blood pressure, median (IQR)	114 (107, 120)	115 (105, 128)	0.17
Hemoglobin A1c (median, IQR)	5.4 (4.1, 5.9)	5.3 (5.0, 5.7)	0.48
Smoking history (n, %)			0.30
Never	27 (48%)	136 (54%)	
Former	18 (32%)	87 (34%)	
Current	11 (20%)	30 (12%)	
Body mass index, median (IQR)	20.9 (18.6, 24.6)	22.0 (19.7, 25.2)	0.10