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ORIGINAL RESEARCH

Cardiovascular Disease Burden in Rural Africa: Does HIV and Antiretroviral Treatment Play a Role?

Baseline Analysis of the Ndlovu Cohort Study

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BACKGROUND: HIV is associated with an increased risk of cardiovascular disease (CVD) in high-income countries. Little is known about the CVD burden in sub-Saharan Africa, where 70% of the world's HIV-positive population lives. This study aims to provide insight into the burden of CVD risk in a rural setting in sub-Saharan Africa considering HIV infection and antiretroviral therapy (ART).

METHODS AND RESULTS: A cross-sectional analysis was conducted of the baseline of the Ndlovu Cohort study including HIV-negative and HIV-positive participants in rural South Africa between 2014 and 2017. Information was collected on demographics, socioeconomic status, and CVD risk factors. Carotid intima-media thickness measurement was performed. The influence of HIV and ART on the burden of CVD was determined by comparing HIV-positive participants who were ART naive on first-line or second-line ART with HIV-negative participants. In total, 1927 participants were included, of whom 887 (46%) were HIV positive and 54% women. The median age was 38 years. Overall, 690 participants (79%) were on ART, with 613 (89%) on first-line and 77 (11%) on second-line therapy. Participants with HIV had lower values for most of the CVD risk factors but higher C-reactive protein levels than HIV-negative participants. ART-naive, HIV-positive participants had similar carotid intima-media thickness compared with HIV-negative participants but carotid intima-media thickness was increased for participants on ART aged 30 years and older compared with HIV-negative participants.

CONCLUSIONS: HIV-positive participants presented with a favorable CVD risk profile compared with HIV-negative participants. However, carotid intima-media thickness was increased in HIV-positive participants on ART, indicating a higher burden of subclinical CVD for the HIV-positive population.

Key Words: cardiovascular disease ■ carotid intima-media thickness ■ HIV ■ sub-Saharan Africa

Nearly 70% of all HIV-infected people reside in sub-Saharan Africa (SSA).[1] The successful rollout of antiretroviral therapy (ART) has changed HIV from a life-threatening illness to a chronic condition. Life expectancy for people living with HIV has increased substantially.[2] As a result, the healthcare system will be faced with an aging HIV population, and hence with an increasing number of HIV-infected people with comorbidities.[3,4]

Meanwhile the African continent is facing an increasing burden of noncommunicable diseases.[5] Cerebrovascular and ischemic heart disease were, respectively, the fourth and fifth leading causes of life years lost in South Africa in 2015.[6] Simultaneously, a high

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For Sources of Funding and Disclosures, see page 9.

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CLINICAL PERSPECTIVE

What Is New?

- In an urban African population, people with HIV treated with antiretroviral therapy have fewer classical risk factors for cardiovascular disease then people without HIV.
- However, in these patients, carotid intima-media thickness is increased from the age of 30 years compared with non–HIV-infected participants.
- This indicates an increased risk of cardiovascular disease for the aging HIV-positive population on treatment.

What Are the Clinical Implications?

- HIV care should incorporate screening for and treatment of risk factors for cardiovascular disease.
- Treatment thresholds might need to be stricter as people living with HIV seem to have an increased risk of cardiovascular disease.
- This increased risk appears to exist despite a lower level of conventional cardiovascular disease risk factors compared with the HIV-negative population.

Nonstandard Abbreviations and Acronyms

ART	antiretroviral treatment
BP	blood pressure
BMI	body mass index
CIMT	carotid intima-media thickness
CRP	C-reactive protein
CVD	cardiovascular disease
HDL-C	high-density lipoprotein cholesterol
HIC	high-income countries
IMT	intima-media thickness
IQR	interquartile range
LDL-C	low-density lipoprotein cholesterol
MET	metabolic equivalent
PLHIV	people living with HIV
SSA	sub-Saharan Africa

prevalence of classic cardiovascular risk factors such as hypertension, obesity, and smoking was observed.[7,8]

Research from high-income countries (HICs) indicated that HIV infection and ART are independent risk factors for cardiovascular disease (CVD).[9] The situation for SSA is less clear. Conventional CVD risk factor levels appear to be lower for people living with HIV (PLHIV) compared with the general population.[7,8,10] This most likely reflects the differences in demographics between the HIV epidemic in HICs and SSA as the majority of PLHIV in HICs are men who have sex with men and intravenous drug users, while PLHIV in SSA are from the general population and more often women than men.[1] On the other hand, HIV infection and treatment with ART result in ongoing low-grade inflammation and elevation of markers of endothelial damage, which are known contributors to CVD risk.[11,12]

So far, there are no longitudinal studies addressing CVD risk in patients with HIV in SSA, but there are some cross-sectional studies which all show that HIV is associated with a higher risk of CVD or stroke compared with the non–HIV-infected population.[13–15] The role of ART is even less clear than the role of HIV.[12,16] To gain insight into the burden of CVD in HIV infection, surrogate markers for CVD risk have been used, among which is the well-established carotid intima-media thickness (CIMT) measurement.[17] HIV has been associated with an increase in CIMT in HICs[18–21]; however, smaller studies in SSA have not found a relationship between HIV and CIMT.[12,22,23]

The NCS (Ndlovu Cohort Study) was set up to investigate the role of HIV and ART on the burden of cardiovascular risk factors and CVD in a rural African population. This study presents the cardiovascular risk factor profile at baseline and assesses the burden of subclinical CVD using CIMT in PLHIV, whether or not on treatment, in comparison to people without HIV.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The NCS is located in a rural area of Limpopo, South Africa, and included 1040 HIV-negative participants and 887 HIV-positive participants from November 2014 to August 2017. The design and methods have been previously described.[24] Briefly, eligible participants were: (1) aged 18 years or older; (2) able to provide written, informed consent; and (3) committed to long-term follow-up. Participants were recruited through community campaigns, at local events and shopping centers, as well as at the Ndlovu Medical Center (NMC). The NMC included a large rural HIV treatment facility, contracted by the South African Department of Health, providing free-of-charge HIV treatment and follow-up to ≈3700 HIV-positive patients. Participants who tested positive for HIV upon enrollment in our study were referred to the NMC, or any other local HIV treatment facility, to initiate ART.

The study was approved by the Human Research Ethics Committee at the University of Pretoria, Pretoria, South Africa, and the Limpopo Department of Health Ethics Committee, and written informed consent was obtained from all participants before study participation. Upon enrollment, participants underwent

HIV testing unless they were taking HIV treatment. Information was collected on demographics, socioeconomic status, medical history, and medication use (both related to HIV as well as for other medical conditions) using standardized questionnaires. ART treatment status was assessed by self-report and complemented with data from an electronic HIV registry (TIER.net). Tier.net is an online electronic database that monitors HIV and tuberculosis treatment, and it has been implemented in a number of SSA countries including South Africa.[25,26] A participant who was diagnosed with HIV at a maximum of 8 weeks before inclusion was considered to be newly diagnosed and a participant who initiated ART at a maximum of 8 weeks before enrollment was considered to be ART naive. The date of HIV diagnosis and ART use were set to the first of July if only the year was known. If the date of the first ART prescription in TIER.net was before the self-reported date of HIV diagnosis, the date of the first prescription was assumed to also be the date of HIV diagnosis. Smoking, alcohol use, and other cardiovascular risk factors were assessed with a modified version of the World Health Organization's STEPS (STEPwise approach to chronic disease risk factor surveillance) instrument.[27] Family history was considered positive for CVD when a history of stroke and/or heart attack was reported in a first-degree family member (parent or sibling) before the age of 60. Physical activity was assessed with the International Physical Activity Questionnaire.[28] Anthropometric measurements included height, weight, and waist, and hip circumference. Three blood pressure (BP) measurements were obtained after a 5-minute rest. The average of the second and the third measurement was used for the analysis. Hypertension was defined as a systolic BP ≥140 mm Hg and/or a diastolic BP ≥90 mm Hg and/or use of antihypertensive drugs. Blood was drawn for analysis of lipids, glucose, and HIV viral load and CD4+ cell count for all HIV-positive participants. Glycated hemoglobin was added to the analysis some months after the start of the study, and results were available for 1494 (77.5%) of the participants. Diabetes mellitus was defined as random glucose >11 mmol/L or glycated hemoglobin >6.4 mmol/L or the use of blood glucose–lowering medication. In addition, a urine sample was taken for analysis of urine albumin and creatinine. All blood samples were spun the same day and analyzed the next day at an accredited laboratory (TogaLabs, South Africa).

CIMT Measurement

CIMT was measured in all participants after a 15-minute rest using a Siemens Acuson p300 ultrasound (Siemens Healthcare [Pty] Ltd, South Africa). Scans were obtained in B mode with a ≥7.0 MHz linear probe. The near wall and far wall of the common carotid artery (CCA) were measured at 3 standardized angles at both the right and left side using a Meijer carotid Arc.[29] The far walls of the carotid bulb on the right and left sides were captured at the best visible angle. CIMT was measured semiautomatically with Artery Measurement System software (Chalmers University, Gothenburg, Sweden) and adjusted manually if needed. Analyses were performed in batch with a uniform reading protocol by 3 readers who were blinded to the HIV status of the participant. The inter-reading agreement for the readers was excellent for mean CCA–intima-media thickness (IMT) and good for maximum CCA-IMT (0.93 and 0.87, respectively).[30] CIMT reading included mean and maximum thickness of the intima-media layer of the near and far wall across all 6 angles of the CCA (mean CCA-IMT and maximum CCA-IMT), and the maximum IMT at the carotid bulb left and right (maximum bulb-IMT). A mean CCA-IMT of >1.0 mm at any of the measured angles was considered as a plaque.[31]

Statistical Analysis

Descriptive data were presented as mean (SD), median (interquartile range), or count (percentage), as appropriate. Baseline characteristics and CIMT outcomes were presented by HIV and ART status. Cardiovascular risk factors were compared across groups (HIV negative, HIV positive, ART naive, or taking first- or second-line ART) using the HIV-negative group as the reference group while adjusting for sex and age.

A total of 43.3% of the BP readings were regarded as missing data as these measurements were taken with a nonvalidated BP device (all BP data obtained in 2016 and 2017). These data were regarded to be missing at random. Multiple imputation was performed using a Markov chain Monte Carlo approach with starting values based on an expectation-maximization estimate, resulting in 20 imputed data sets. All valid baseline BP measurements, BP measurements from year 2 and 3 follow-up, HIV status, ART status, age, sex, education, smoking, alcohol, body mass index (BMI), waist-hip ratio, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, physical activity, Patient Health Questionnaire-9, use of antihypertensive drugs, family history for CVD, and CD4 cells counts were included in the imputation model. Multiple imputation was performed using SAS version 9.4 (SAS Institute Inc). For the analyses described below, each of the 20 data sets were analyzed and the pooled estimates per model are presented.

As previous research suggested that the effect of HIV on CIMT could be age dependent,[32] we first tested whether there was an interaction between age and HIV on CIMT in our data. This interaction turned out to be positive, and therefore the analysis was stratified in 3

age categories: 18 to 29 years, 30 to 49 years, and 50+ years. Participants on first- and second-line ART were regrouped to "HIV positive on ART" as the relatively small number of participants on second-line ART (n=77) did not allow a separate analysis on second-line ART in the different age strata. The influence of HIV and ART on mean CCA-IMT, maximum CCA-IMT, and maximum bulb-IMT values were analyzed in a linear regression analysis while using the HIV-negative group as a reference group. The first model was adjusted for age and sex and the second model was additionally adjusted for known contributors to CIMT, namely smoking, systolic BP, BMI, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and glucose.[29] Finally, a possible mediation effect of systolic BP, BMI, lipids, and glucose was tested by running the forth model while excluding the variables one by one in consecutive models.

We repeated all of these steps for HIV-positive participants only, using the ART-naive group as the reference group. The final model was additionally adjusted for CD4 cell count, viral load, known duration of HIV infection, and time on ART. The influence of viremia (either between 50 to 1000 copies or >1000 cp/mL) on viral load was tested in a linear regression while using the group with undetectable viral load (<50 cp/mL) as a reference group. Finally, we analyzed the influence of HIV and ART on mean CCA outcomes for men and women separately. Statistical analyses other than creation of multiple imputed data sets were performed using IBM SPSS Statistics version 25.

RESULTS

A total of 1927 participants were recruited: 1056 (55%) were women and 887 (46%) were HIV positive. The median age of the total population was 38 years. HIV-negative participants were significantly younger than the HIV-positive participants (32 years versus 41 years, $P<0.001$). The majority of the population was unemployed and lived under the poverty line, defined as a monthly income <648 South African rand (≈$46).[33] Sixty-one percent of the HIV-negative group versus 55% of the HIV-positive group was in a stable relationship ($P=0.004$) (Table 1). In total, 387 (20%) of all participants had hypertension, of whom 125 (32%) were taking antihypertensive therapy and 91 (5%) had diabetes mellitus, of whom 39 (43%) were using treatment (Table 2).

People with HIV knew their diagnosis for about 5 years, ranging from zero weeks for newly diagnosed participants to >10 years for some participants on second-line ART. Only about 65% of all participants were virally suppressed, including 16% of the ART-naive participants (Table 3). More than 90% of participants on first-line ART were using the recommended first-line ART regimen tenofovir, emtricitabine, and efavirenz. The majority of participants on second-line ART were using ritonavir-boosted lopinavir.

Systolic and diastolic BP, BMI, glucose, glycated hemoglobin, total cholesterol, and low-density lipoprotein cholesterol were lower in HIV-positive participants compared with HIV-negative participants following adjustment for age and sex (see Table 4 for a comparison between the treatment groups). On the contrary, C-reactive protein was significantly higher for PLHIV compared with the HIV-negative group ($P<0.001$).

Mean and maximum CCA-IMT was available for 1775 (92%) and maximum bulb-IMT for 1596 (83%) of the participants. Plaques (mean CCA-IMT >1 mm) were present in 87 (4.5%) of the participants, and this prevalence was not different between HIV-positive and HIV-negative participants following correction for age and sex ($P=0.46$).

After adjustment for age and sex, mean CCA-IMT did not differ between the groups (Table 5).

Following adjustment for conventional CVD risk factors, mean CCA-IMT was higher in HIV-positive participants on ART aged 30 years and older, and this effect increased with age (β=0.015 [$P=0.009$] in the age group 30 to 49 years versus β=0.050 [$P<0.001$] in the age group of 50 years and older).

There was no indication for mediation by high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, BMI, systolic BP, or glucose as excluding these variables from the model one by one did not alter the magnitude or direction of the findings. Exclusion of all HIV-positive, ART-naive participants with a suppressed viral load from the analysis did not change the findings either. The contribution of CVD risk factors to mean CCA-IMT increased with age (Table 6).

The effects of HIV, ART, and CVD risk factors on maximum CCA-IMT had the same direction and magnitude. Maximum bulb-IMT did not differ by HIV and ART status in any of the age strata, and adjustment for age, sex, and CVD risk factors did not change this finding.

To investigate the influence of HIV characteristics on mean CCA-IMT HIV-positive participants were analyzed separately. Time on ART was associated with a higher CCA-IMT in the age group 30 to 49 years (β=0.006 per year of use, $P<0.001$), while years since HIV diagnosis was associated with lower CCA-IMT (β=−0.005 per year since diagnosis, $P=0.001$). Viral load was not associated with mean CCA-IMT, but an increase in CD4+ cell count was associated with a lower mean CCA-IMT (β=−0.004 per increase with 100 cells/mm^3, $P=0.01$). Using maximum CCA-IMT as the outcome, the same trends were seen in the age group 30 to 49 years. None of the HIV-related variables were associated with mean or maximum CCA-IMT in the age group 50 years and older.

Finally, mean CCA-IMT results were analyzed for men and women separately. Following adjustment

Table 1. Baseline Description I

	HIV Negative (n=1040)	ART Naive (n=197)	HIV Positive, First-Line ART (n=613)	Second-Line ART (n=77)
Demographics and socioeconomic background				
Age, median (IQR), y	32.0 (24.0–48.0)	35.0 (28.0–45.0)	41.0 (36.0–49.0)	43.0 (37.5–49.5)
Women	527 (50.7)	124 (62.9)	362 (59.1)	43 (55.8)
Highest level of education				
None	42 (4.0)	5 (2.5)	31 (5.1)	4 (5.2)
Primary	179 (17.2)	48 (24.4)	130 (21.2)	21 (27.3)
Secondary and matric	711 (68.4)	125 (63.5)	419 (68.4)	45 (58.4)
College and university	108 (10.4)	19 (9.6)	33 (5.4)	7 (9.1)
Employment				
Unemployed	696 (66.9)	150 (76.1)	408 (66.6)	53 (68.8)
Self-employed	159 (15.3)	34 (17.3)	185 (30.2)	22 (28.6)
Other (student, retired, volunteer)	185 (17.8)	13 (6.6)	20 (3.3)	2 (2.6)
Income per person per mo in rands* (n=1824)				
<648	621 (62.8)	125 (66.8)	349 (60.7)	48 (65.8)
648 to 992	79 (8.0)	12 (6.4)	49 (8.5)	4 (5.5)
>992	289 (29.2)	50 (26.7)	177 (30.8)	21 (28.8)
Stable relationship (married, life partner, cohabiting)	638 (61.3)	91 (46.2)	351 (57.3)	44 (57.1)
Cardiovascular risk factors				
Alcohol use, ever	777 (74.7)	154 (78.2)	378 (61.7)	49 (63.6)
Alcohol use in the past 30 d	406 (39.0)	69 (35.0)	154 (25.1)	23 (29.9)
Smoker (n=1923)				
Ever	459 (44.1)	83 (42.1)	214 (35.0)	30 (39.0)
Current	334 (32.1)	58 (29.4)	128 (20.9)	18 (23.4)
Cigarettes/cigars per d median (IQR), No.	6.0 (4.0–10.0)	6.0 (4.0–11.5)	6.0 (4.0–10.0)	4.5 (4.0–9.3)
Positive family history for CVD	35 (3.4)	4 (2.0)	8 (1.3)	0
Physical activity, MET-min/wk				
Moderate	401 (38.6)	73 (37.1)	187 (30.5)	26 (33.8)
High	302 (29.0)	48 (24.4)	124 (20.2)	18 (23.4)

ART indicates antiretroviral therapy; CVD, cardiovascular disease; IQR, interquartile range; and MET, metabolic equivalent task.
*Lower bound poverty line: <648, upper bound poverty line: >992. Data are expressed as mean (SD) or count (percentage) unless otherwise specified.

for CVD risk factors, the same trends were observed with a higher CCA-IMT for participants on ART compared with HIV-negative participants in the age category 30 to 49 years and, for men only, 50 years and older.

DISCUSSION

In this large study comparing PLHIV whether or not on ART with HIV-negative participants, PLHIV had favorable levels of most conventional CVD risk factors compared with HIV-negative participants. HIV itself seemed not to be associated with increased CCA-IMT, but treatment with ART was associated with an increase in CCA-IMT in people 30 years and older, and this effect increased with age. The influence of conventional CVD risk factors on CCA-IMT also increased with age.

Lower levels of conventional CVD risk factors in PLHIV compared with the HIV-negative group is in contrast to studies from HICs reporting a higher burden of CVD risk factors in the HIV-positive compared with the HIV-negative population.[34,35] Our findings are, however, in line with 2 meta-analyses including studies from SSA only[10,36] as well as with more recent population-based surveys in South Africa.[7,12] This likely reflects the differences in sex distribution and lifestyle between the HIV-positive population in HICs compared with SSA. The

Table 2. Baseline Description II

	HIV Negative (n=1040)	ART Naive (n=197)	HIV Positive, First-Line ART (n=613)	Second-line ART (n=77)
Physical examination				
Average systolic BP, mm Hg*	120.1 (24.1)	115.5 (21.5)	114.1 (20.5)	116.8 (17.8)
Average diastolic BP, mm Hg*	74.8 (14.2)	74.5 (12.7)	73.3 (13.1)	74.0 (12.5)
BMI, median (IQR) kg/m^2	23.1 (19.8–28.3)	22.5 (19.3–26.9)	22.8 (19.6–26.5)	22.1 (19.1–26.9)
Waist circumference, cm	82.7 (13.9)	82.2 (12.8)	85.5 (12.5)	83.6 (12.3)
Hip circumference, cm	99.4 (14.0)	99.6 (14.1)	99.9 (13.3)	98.5 (15.6)
Laboratory analysis				
Fasting glucose, mmol/L (n=1912)	5.02 (2.65)	4.73 (1.34)	4.89 (1.16)	4.89 (1.39)
HbA_{1c}, % (n=1495)	5.58 (0.88)	5.52 (0.38)	5.62 (0.66)	5.49 (0.66)
Total cholesterol, mmol/L (n=1909)	4.19 (1.01)	3.88 (0.91)	4.38 (0.99)	4.31 (1.09)
HDL-C, mmol/L (n=1909)	1.38 (0.34)	1.26 (0.37)	1.49 (0.42)	1.44 (0.51)
LDL-C, mmol/L (n=1904)	2.32 (0.89)	2.18 (0.77)	2.35 (0.86)	2.26 (0.83)
Triglycerides, median (IQR), mmol/L	0.90 (0.60–1.30)	0.90 (0.65 –1.20)	1.00 (0.80–1.50)	1.10 (0.73–1.70)
CRP, median (IQR), mg/L	3.0 (2.0–6.0)	3.0 (2.0–13.0)	5.0 (2.0–11.0)	4.0 (2.0–9.8)
Urine albumin/creatinine ratio, median (IQR), mg/mmol	0.65 (0.43–1.26)	0.85 (0.55–1.55)	1.05 (0.59–2.26)	0.82 (0.55–1.64)
Carotid IMT outcomes				
Mean CCA-IMT, median (IQR), mm (n=1774)	0.565 (0.510–0.660)	0.555 (0.509–0.629)	0.610 (0.541–0.696)	0.630 (0.547–0.694)
Maximum CCA-IMT, median (IQR), mm (n=1774)	0.645 (0.571–0.759)	0.637 (0.573–0.722)	0.693 (0.613–0.800)	0.712 (0.636–0.800)
Maximum bulb-IMT, median (IQR), mm (n=1595)	0.781 (0.649–0.942)	0.773 (0.636–0.942)	0.848 (0.719–1.009)	0.852 (0.723–1.026)
Plaque (mean CCA-IMT >1 mm)	44 (4.2)	3 (1.5)	34 (5.5)	6 (7.8)

Data are expressed as mean (SD) or count (percentage) unless otherwise specified. ART indicates antiretroviral therapy; BMI, body mass index; BP, blood pressure; CCA, common carotid artery; CRP, C-reactive protein; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; IQR, interquartile range; and LDL-C, low-density lipoprotein cholesterol.

*Based on the imputed data sets.

fact that a large proportion of HIV-positive individuals in SSA are relatively young may obscure any adverse effects on cardiovascular risk with advancing age.

The influence of HIV on CIMT was observed to vary across the lifespan, with a higher CCA-IMT for people on ART from the age of 30 years compared with HIV-negative individuals. This effect seems to be driven by ART rather than by HIV as time since HIV diagnosis was associated with a decrease in CCA-IMT, but the time on ART with an increase in CCA-IMT. The age dependency of the influence of HIV and ART on CIMT was also described in a meta-analysis by Hanna et al.[32] They found higher CIMT values for the HIV-positive participants aged 6 to 29 years compared

Table 3. HIV-Related Characteristics

	ART Naive (n=197)	First-Line ART (n=612)	Second-Line ART (n=77)
Time since HIV diagnosis, mo (n=881)	0.0 (0.0–7.0)	67.0 (30.0–102.0)	99.0 (70.5–126.5)
Newly diagnosed upon enrollment, No. (%)* (n=881)	139 (72.4)	0	0
Time on ART, mo	…	59.0 (21.0–97.0)	97.0 (59.0–122.5)
Of which time on second-line ART	…	…	42.0 (15.5–54.8)
CD4+ cell count, cells/mm^3 (n=873)	399 (275–553)	494 (338–679)	467 (330–647)
CD4+ <200, cells/mm^3, No. (%)	36 (18.6)	51 (8.3)	8 (10.5)
Viral load, cp/mL, No. (%) (n=872)			
<50	30 (15.5)	492 (81.7)	45 (59.2)
50 to 1000	26 (13.4)	47 (7.8)	14 (18.4)
>1000	138 (71.1)	63 (10.5)	17 (22.4)

ART indicates antiretroviral therapy.

*Diagnosed within 8 weeks before enrollment. Data are expressed as median (interquartile range) or count (percentage).

Table 4. CVD Risk Factors According to HIV and ART Corrected for Sex and Age

	HIV Negative			HIV Positive			
		ART Naive (n=197)		First-Line ART (n=613)		Second-Line ART (n=77)	
		β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Systolic BP, mm Hg*	Reference	−4.27 (−8.04–0.50)	0.027	−8.12 (−10.57–5.67)	<0.001	−8.93 (−13.57–2.29)	0.006
Diastolic BP, mm Hg*	Reference	−0.67 (−3.03–1.70)	0.579	−3.20 (−4.72–1.68)	<0.001	−3.95 (−7.52–0.37)	0.031
BMI, kg/m^2	Reference	−1.49 (−2.33–0.65)	0.001	−1.95 (−2.51–1.38)	<0.001	−1.93 (−3.21–0.65)	0.003
Fasting glucose, mmol/L	Reference	−0.272 (−0.555–0.011)	0.059	−0.197 (−0.384–0.010)	0.039	−0.212 (−0.615–0.191)	0.302
HbA_{1c}, %	Reference	−0.113 (−0.243–0.017))	0.089	−0.120 (−0.206–0.034)	0.006	−0.264 (−0.450–0.079)	0.005
Total cholesterol, mmol/L	Reference	−0.359 (−0.501–0.217)	<0.001	−0.001 (−0.097–0.095)	0.988	−0.090 (−0.309–0.130)	0.423
HDL-C, mmol/L	Reference	−0.118 (−0.175–0.061)	<0.001	0.106 (0.067–0.144)	<0.001	0.013 −0.076–0.101)	0.780
LDL-C, mmol/L	Reference	−0.194 (−0.320–0.068)	0.003	−0.115 (−0.200–0.030)	0.008	−0.214 (−0.408–0.019)	0.031
Log-triglycerides, mmol/L	Reference	−0.043 (−0.122–0.036)	0.287	0.025 (−0.029–0.078)	0.366	0.133 (0.011–0.254)	0.032
Log-CRP	Reference	0.332 (0.179–0.484)	<0.001	0.410 (0.308–0.513)	<0.001	0.210 (−0.025–0.446)	0.080
Current smoking, OR	Reference	1.071 (0.628–1.828)	0.801	0.696 (0.486–0.997)	0.048	0.708 (0.323–1.551)	0.388

β Values represent the difference in mean value, adjusted for age and sex, as compared with the reference group. ART indicates antiretroviral therapy; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and OR, odds ratio.

*Based on the imputed data sets.

with HIV-negative participants and, in the age category 30 years and older, similar CIMT for HIV-positive participants on ART compared with HIV-negative controls. In contrast to these findings, we observed similar CIMT values between PLHIV and HIV-negative participants in the young age category and a higher CIMT in participants on ART aged 30 years and older compared with HIV-negative controls.

Our results are in line with several studies conducted in HICs, which all reported higher CIMT values for PLHIV on ART compared with HIV-negative controls.[20,21,37,38] However, studies conducted in SSA all found equal or lower CIMT values in PLHIV compared with HIV-negative participants.[12,22,23,39] It is challenging to explain why our findings differ from these studies. The average age of participants in these studies was comparable to our study, but these studies were smaller and only one study included participants on second-line ART.[22] Other reasons to consider are differences in time since HIV diagnosis, time on ART, exposure to older ART regimens, and differences in the extent of immune dysregulation. In

Table 5. HIV and ART Status on Mean CCA-IMT (n=1775)

	HIV Negative	HIV Positive, ART Naive	*P* Value	HIV Positive on ART	*P* Value
Model 1					
Age 18 to 29, y (n=500)		−0.004 (−0.021–0.013)	0.604	0.005 (−0.013–0.023)	0.576
Age 30 to 49 y (n=840)	Reference	−0.014 (−0.033–0.004)	0.117	−0.002 (0.013–0.010)	0.777
Age ≥50 y (n=435)		−0.035 (−0.086–0.017)	0.184	0.015 (−0.012–0.043)	0.277
Model 2					
Age 18 to 29 y (n=492)		−0.005 (−0.021–0.012)	0.592	0.011 (−0.007–0.029)	0.245
Age 30 to 49 y (n=834)	Reference	−0.001 (−0.018–0.017)	0.945	0.015 (0.004–0.027)	0.009
Age ≥50 y (n=429)		−0.016 (−0.064–0.033)	0.527	0.050 (0.022–0.077)	<0.001

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, current smoking, systolic blood pressure, body mass index, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting glucose. ART indicates antiretroviral therapy; CCA, common carotid artery; and IMT, intima-media thickness.

Table 6. Association Between CVD Risk Factors and CCA-IMT

	Age 18 to 29 y		Age 30 to 49 y		Age ≥50 y	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Age, y	0.001 (−0.001 to 0.002)	0.422	0.006 (0.005–0.007)	<0.001	0.007 (0.004–0.009)	<0.001
Men	0.024 (0.012–0.037)	<0.001	0.026 (0.013–0.039)	<0.001	0.077 (0.049–0.105)	<0.001
Current smoking	−0.001 (−0.014 to 0.012)	0.849	−0.001 (−0.015 to 0.013)	0.863	0.002 (−0.028 to 0.031)	0.906
Systolic BP, mm Hg	+0.000 (0.000–0.001)	0.072	0.001 (0.000–0.001)	<0.001	0.001 (0.001–0.002)	<0.001
BMI, kg/m^2	0.003 (0.001–0.004)	<0.001	0.003 (0.002–0.004)	<0.001	0.003 (0.000–0.005)	0.035
HDL-C, mmol/L	−0.007 (−0.023 to 0.008)	0.343	−0.001 (−0.015 to 0.012)	0.833	−0.040 (−0.073 to 0.008)	0.015
LDL-C, mmol/L	0.000 (−0.007 to 0.007)	0.934	0.009 (0.003–0.015)	0.005	0.033 (0.020–0.046)	<0.001
Glucose, mmol/L	0.005 (0.001–0.010)	0.029	0.004 (0.000–0.007)	0.030	0.005 (0.001–0.010)	0.010

Linear regression analysis including HIV and treatment status and all of the above-mentioned variables. BMI indicates body mass index; BP, blood pressure; CCA, common carotid artery; CVD, cardiovascular disease; IMT, intima-media thickness; HDL-C, high-density lipoprotein cholesterol; and LDL-C, low-density lipoprotein cholesterol.

our cohort, 35% of PLHIV had detectable viremia, and the accompanying immune activation was reflected by the higher C-reactive protein levels for PLHIV compared with the HIV-negative participants. Both viremia and immune activation are known risk factors for CVD.[40–42] However, this might not explain everything as most of the studies in SSA also included HIV-positive, ART naive participants, and our analysis suggests that CIMT is mainly driven by ART and not by HIV. Given the large sample size and the inclusion of a representative HIV-negative control group in the current study, we believe that the current results reliably reflect the effect of HIV and ART on CIMT in this rural African setting.

Study Limitations

Some limitations of this study need to be mentioned. A material proportion of the BP values were imputed as we could not use the original data. We assumed data to be missing completely at random so it is unlikely that this affects the comparison between the groups, but it limits the ability to state something about the prevalence of hypertension in our population. There is a remarkably high percentage of HIV-positive, ART-naive participants with undetectable viral load. This may reflect nondisclosure about HIV status and use of ART and this may have diminished differences between the ART-naive group and participants on ART. However, excluding these participants from the analysis did not change the findings. Of concern is the high percentage of PLHIV with detectable viremia (18% of participants on first-line ART and 41% of participants on second-line ART). Apart from the clinical implications, it might limit the generalizability of our results to settings with higher rates of viral suppression. Finally, we could present CVD risk profile by ART line (first- or second-line), but, upon stratification, the number of participants on second-line ART per group was too small to include separately in the analysis of CIMT.

CONCLUSIONS

Our data suggest that the older HIV-positive population on ART has a higher risk of CVD than the HIV-negative population as estimated from the carotid artery wall thickness. Results from prospective studies addressing CVD end points are needed to confirm this finding. The NCS will contribute to understanding the effects of HIV on the burden of CVD in the long term. The first participants in our cohort have now completed 4 years of follow-up. In future publications we will address change in CIMT over time between HIV-positive and HIV-negative participants, as well as CVD end points. In the meantime, HIV care should incorporate screening for and treatment of risk factors for CVD, and treatment thresholds might need to be stricter as PLHIV seem to have an increased risk of CVD despite a lower level of conventional CVD risk factors compared with the HIV-negative population.

APPENDIX

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ARTICLE INFORMATION

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Disclosures

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