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Clinical short communication

Lack of impact of HIV status on carotid intima media thickness in a cohort of stroke patients in South Africa

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ABSTRACT

Introduction: People living with HIV (PLWH) are at increased risk for cardiovascular disease. Carotid intima media thickness (cIMT) is a validated surrogate marker of atherosclerosis, and an accurate predictor of future cardiovascular events. It is uncertain whether HIV potentiates stroke risk through atherosclerosis in Sub-Saharan Africa and what effect HIV status has on cIMT. We sought to investigate the relationship between HIV status and cIMT in stroke patients in a region that is burdened with dual epidemics of HIV and stroke in the young.
Methods: Consecutive patients with new onset ischaemic stroke were recruited from a quaternary-level hospital in Johannesburg, South Africa, from August 2014 to November 2017. Patients were assessed for the presence of traditional cardiovascular risk factors and HIV infection, and investigated for stroke aetiology. cIMT was measured using high resolution B-mode ultrasound following standardized techniques.
Results: 168 patients were included in the study, of which 62 (36.9%) were PLWH. Mean cIMT was higher in HIV-uninfected patients when compared to PLWH (0.79 ± 0.19 mm vs 0.69 ± 0.18 mm, $p = 0.0021$). However after adjusting for age, sex, hypertension, diabetes mellitus, smoking, total cholesterol, body mass index and stroke aetiology, there was no difference in mean cIMT between the groups (0.76 ± 0.16 mm vs 0.73 ± 0.17 mm, $p = 0.29$). Regression models revealed the determinants of cIMT to be age ($p < 0.0001$), hypertension ($p = 0.0098$) and total cholesterol ($p = 0.005$), while the determinants of increased cIMT (≥0.70 mm) were only age ($p < 0.0001$) and hypertension ($p = 0.0002$).
Conclusion: HIV status had no effect on cIMT in our cohort of stroke patients. The main determinants of cIMT were age and hypertension.

1. Introduction

People living with HIV (PLWH) are twice as likely to develop cardiovascular disease, including stroke, compared to uninfected individuals. [1] Proposed mechanisms for this include accelerated atherosclerosis secondary to chronic inflammation and immune activation in an aging population, as well as the atherogenic effects of traditional cardiovascular risk factors (TRFs) and the metabolic side effects of longstanding antiretroviral therapy (ART), particularly protease inhibitors (PIs). [2]

Carotid intima media thickness (cIMT) has been widely investigated and validated as a surrogate marker of atherosclerosis and is regarded as an accurate predictor of future cardiovascular events. [3] Its non-invasive, inexpensive technique makes it a valuable risk prediction tool. Evidence for the association between HIV status and cIMT is not conclusive, although data from high-income countries (HICs) suggest a moderately higher cIMT in PLWH when compared to uninfected controls, after adjusting for TRFs. [4]

Over 80% of the world's PLWH reside in low-to-middle income countries (LMICs), particularly in Sub-Saharan Africa (SSA). [5] South Africa itself is home to the greatest number of PLWH in the world (8.5 million people). [6] While data from HICs, based on a very small proportion of the world's PLWH population, is often extrapolated globally due to a paucity of local data, it is not always applicable. It is unknown

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what effect HIV status has on cIMT in a LMIC population where stroke patients are much younger, have fewer TRFs, less ART-exposure and often have alternative, non-atherosclerotic stroke aetiologies when compared to those in HICs. [7,8]

We thus sought to investigate the relationship between HIV status and cIMT in stroke patients from a LMIC at the epicentre of the world's HIV epidemic, and to establish what the determinants of cIMT are in this population.

2. Methods

This cross-sectional study took place at the Charlotte Maxeke Johannesburg Academic Hospital, a 1000-bed quaternary-level hospital in Johannesburg, South Africa, from August 2014 to November 2017 (40 months).

We recruited consecutive patients aged 18 years and older who presented with a new onset ischaemic stroke. Stroke was defined as per the World Health Organization case definition. [9] Exclusion criteria were the diagnosis of meningitis based on cerebrospinal fluid examination, evidence of opportunistic infections, the presence of intracranial mass lesions on radiographic imaging, or other stroke mimics. Full informed consent was obtained as per the Helsinki Declaration. Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Certificate number M140429, renewed as M190688).

All patients were assessed and examined by the same specialist neurologist (ES), who co-ordinated and interpreted all relevant investigations and assigned a stroke aetiology according to the Trial of Org 10,172 in Acute Stroke (TOAST) Classification. [10]

Hypertension (HT) was defined as having 3 or more blood pressure readings >140/90 mmHg beyond the first 72 h post-stroke, with or without the presence of the following target organ damage: hypertensive retinopathy on direct ophthalmoscopy, left ventricular hypertrophy on electrocardiogram, echocardiogram or chest X-ray, or renal dysfunction with no other cause. Acute post-stroke elevated blood pressure (BP) was not used as diagnostic for HT due to the well-described transient increase in BP seen acutely post-stroke. [11]

Diabetes mellitus (DM) was defined as a fasting glucose ≥7.0 mmol/l, or a random glucose ≥11.1 mmol/l, or an HbA1c >6.5%. Patients with anaemia were not diagnosed as diabetic solely on HbA1c measurement, to avoid false positives. [12]

Dyslipidaemia was defined as a total cholesterol ≥5.2 mmol/L, and/or low density lipoprotein cholesterol (LDL) ≥ 3.3 mmol/L. [13] Blood for lipogram assessment was taken in a non-fasting state. Current evidence suggests that for cardiovascular risk assessment, non-fasting total cholesterol, and LDL are equivalent to a fasting sample. [13–16] Acute post-stroke transient decreases in cholesterol levels were accounted for by taking blood for lipograms within 24 h of the stroke onset, where possible, and by not considering a low post-stroke high density lipoprotein cholesterol (HDL) to be diagnostic for dyslipidaemia. [17–19]

Body mass index (BMI) was obtained by measuring the patient's height using a stadiometer and the weight using a calibrated mechanical column scale where BMI = weight ÷ height^2. This was not possible in patients unable to stand unaided.

Investigations for stroke aetiology included CT and/or MRI of the brain, CT angiography of the brain, neck and aortic arch, 12-lead electrocardiogram, transthoracic and/or transoesophageal echocardiogram and the full protocol of laboratory investigations as described in the online supplement (Appendix A). HIV testing (ELISA) was performed in all consenting patients, and all PLWH had a CSF examination unless contra-indicated.

cIMT was measured by carotid doppler studies which were performed by a single operator using high resolution B-mode ultrasound (SonoCalc IMT, Sonosite Inc., Bothell, Washington) employing a linear array 7.5 MHz probe as described previously. [20] Images of at least 1 cm length of the far wall of the distal portion of the right common carotid artery from an optimal angle of incidence (defined as the longitudinal angle of approach where both branches of the internal and external carotid artery are visualized simultaneously) at least 1 cm proximal to the flow divider were obtained. cIMT measurements were determined using semi-automated border-detection and quality control software. A total of 6 separate measurements (3 on each side) were averaged to a single mean cIMT. All images were saved electronically, allowing for later quality control and re-evaluation if necessary. A cIMT ≥0.70 mm was considered to be pathological, and suggestive of subclinical atherosclerosis, as per previously published data. [21,22] Patients whose cIMT data were of insufficient quality were excluded from the study.

2.1. Statistical methods

Data was analysed using SAS software, version 9.4 (The SAS Institute, Cary, NC). Continuous variables were evaluated for normality using Shapiro-Wilk and Kolmogorov-Smirnov tests. To compare data between groups, unpaired Student's *t*-test, Chi squared test, and Mann Whitney *U* test were then performed for parametric and non-parametric variables where appropriate. To identify the determinants of cIMT, univariate and multivariate regression analysis was performed. Logistic regression analysis was performed to identify the determinants of increased cIMT. Continuous data were reported as mean ± SD for parametric, or median and interquartile range for non-parametric data. Only available data was analysed. Missing data was not imputed. *P* values <0.05 were considered significant.

3. Results

168 patients were included in the study. (See Fig. 1 for study flowchart). HIV-uninfected patients (n = 106, 63.1%) were older and had more traditional risk factors (HT, DM, higher total cholesterol and higher BMI) than PLWH (n = 62, 36.9%). (Table 1). The only other baseline difference between the two groups was in stroke aetiology (higher proportion of strokes of 'other' aetiology in PLWH). (Table 1).

The mean cIMT (Fig. 2A, HIV-uninfected: 0.79 ± 0.19 mm; PLWH: 0.69 ± 0.18 mm, p = 0.0021), and proportion with increased cIMT (Table 1) were higher in HIV-uninfected patients. However after adjusting for age (Fig. 2B, HIV-uninfected: 0.76 ± 0.15 mm; PLWH: 0.74 ± 0.15 mm, p = 0.35), and adjusting for age, sex, HT, DM, BMI, smoking, total cholesterol and stroke aetiology (Fig. 2C), there was no difference in cIMT between HIV-uninfected and PLWH (0.76 ± 0.16 mm vs 0.73 ± 0.17 mm, p = 0.29).

Multivariate linear regression analyses revealed that the only determinants of cIMT were age, HT and total cholesterol, (Table 2), while multivariate logistic regression analyses showed that the only determinants of an increased cIMT (≥0.70 mm) were age and HT. (Table 2 and Fig. 3). HIV status had no effect on cIMT. Similar results were noted with regression models which excluded stroke aetiology, or included dyslipidaemia instead of total cholesterol, or used median number of risk factors instead of HT, DM, smoking, dyslipidaemia and BMI individually (with and without stroke aetiology) in the model (see Appendix B - Table S1).

3.1. Effect of ART

Of the 62 PLWH, 29 were on ART at the time of stroke. 27 of these were on a fixed-dose combination comprising emtricitabine, tenofovir and efavirenz, while only 2 patients were on a PI-containing regimen. There were no differences in demographics, TRFs, and mean CD4 between ART-exposed and ART-naïve PLWH. (Table 3) Mean cIMT was also similar between the 2 groups. (Table 3). On multivariate regression analyses, the main determinants of cIMT in PLWH were age and sex (Table 4), while age and HT were the main determinants of increased cIMT (≥0.70 mm) (Table 5). ART usage was neither associated with

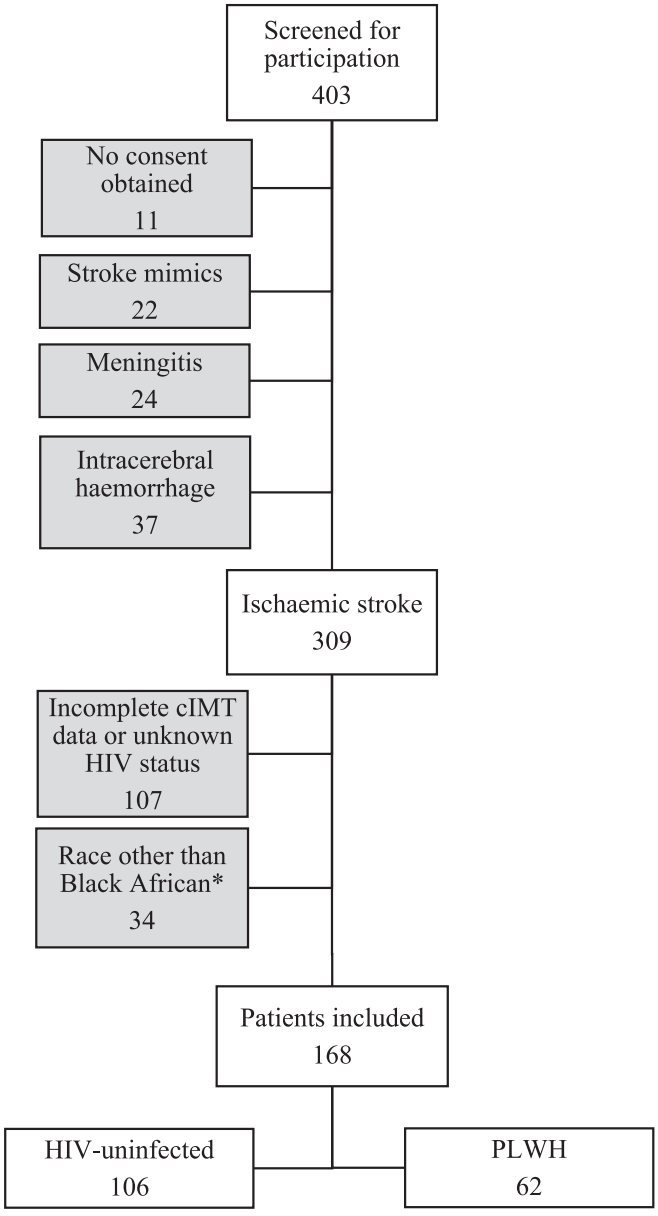

Fig. 1. Study flowchart.
cIMT, carotid intima media thickness; PLWH, people living with HIV.
Groups excluded from the study are shaded in grey.
*In order to mitigate for differences in cIMT reference values in different races, we only analysed the most common racial group (Black African).

cIMT nor an increased IMT in PLWH (Tables 4 and 5).

4. Discussion

We have demonstrated in stroke patients that mean cIMT was similar in PLWH and HIV-uninfected after adjusting for demographics, TRFs and stroke aetiology. The main determinants of cIMT were age and HT, with a lesser role played by total cholesterol. HIV status had no effect on cIMT in our cohort of stroke patients from the epicentre of the world's HIV epidemic.

Previous studies on the effect of HIV status on cIMT have yielded inconsistent results. While some have shown evidence of an increased cIMT in PLWH when compared to uninfected controls [23–27], others have shown no association [28–32] while others have only shown associations in certain groups of patients, including certain age categories. [33]

Table 1
Comparing traditional risk factors and cIMT in PLWH and HIV-uninfected stroke patients.

	PLWH (n = 62)	HIV-uninfected (n = 106)	P value
Age (years)	42.8 ± 12.2	51.8 ± 15.6	0.0002
Male (%)	51.6	43.4	0.30
HT (%)	43.6	65.1	0.01
DM (%)	4.8	22.6	0.002
Dyslipidaemia (%)	29.5 (*n* = 61)	37.5 (*n* = 104)	0.30
Total cholesterol (mmol/L)	4.09 ± 0.91 (n = 61)	4.41 ± 1.11 (n = 104)	0.06
LDL cholesterol (mmol/L)	2.60 ± 0.84 (*n* = 60)	2.78 ± 0.93 (n = 104)	0.21
BMI (kg/m^2)	27.5 ± 6.4 (*n* = 50)	30.5 ± 8.8 (*n* = 96)	0.03
Smoking (%)	27.4	17.0	0.11
Stroke aetiology			0.0002
Cardioembolic (%)	16.1	31.1	
Large vessel atherosclerosis (%)	6.5	3.7	
Small vessel disease (%)	17.7	20.8	
Undetermined (%)	25.8	36.8	
Other (%)	33.9*	7.6**	
Increased cIMT (≥0.70 mm) (%)	35.5	67.9	<0.0001

BMI, body mass index; DM, diabetes mellitus; HT, hypertension; LDL, low density lipoprotein cholesterol; PLWH, people living with HIV.
* including non-atherosclerotic vasculopathy (*n* = 11), HIV-associated vasculitis (*n* = 6), stroke due to recreational drug usage (*n* = 2) and non-lacunar small vessel vasculopathy (*n* = 2).
** including autoimmune vasculitis (*n* = 5), stroke due to hypercoagulable state (n = 2) and stroke due to recreational drug usage (n = 1).

A meta-analysis of 26 studies [4], and another large study [23] not part of this prior meta-analysis, have suggested that the TRF-independent effects of HIV on cIMT are modest at best (0.02 to 0.06 mm higher in PLWH). The meta-analysis reported evidence of publication bias ($p = 0.001$), with smaller studies being more likely to report an increased cIMT in PLWH when compared to larger studies, which mostly showed minimal or no effect. [4] There was also significant heterogeneity between studies ($I^2 = 86.5\%$) and evidence of confounding.

Strikingly, most of this data comes from HICs, where the profile of PLWH differs markedly from LMICs. PLWH in HICs are generally older, with more TRFs and exposure to ART for longer periods when compared to PLWH in LMICs. [34] They also have higher proportions of recreational drug users and men who have sex with men than cohorts from LMICs. A large multinational study from 4 African countries (Burkina Faso, Kenya, Ghana and South Africa) examined cIMT in 8872 patients and reported an inverse association of HIV status with cIMT (β = −8.86 95% CI -15.7 to −2.03). [35] No convincing explanation was offered by the authors for this unexpected finding but may again be indicative of a distinct patient profile in SSA in contrast to HICs. Other cohorts from SSA all reported no effect of HIV status on cIMT. [28–31,36,37]

Importantly, all of these studies have been in non-stroke patients, which makes our study unique. To our knowledge there is no previously published data on cIMT in PLWH who have suffered a stroke. A comprehensive literature search on cIMT, HIV and stroke revealed only 2 publications of potential relevance, both of which used stroke as an outcome measure. Sarfo et al. [38] prospectively followed up 255 ART-exposed Ghanian PLWH for 12 months, during which time 3 PLWH had a stroke. Carotid bulb IMT was independently associated with stroke occurrence (aHR 12.23 (1.28–117.07). However there were no HIV negative controls, thus no inferences can be made on the effect of HIV on cIMT and stroke outcomes.

The metabolic side effects of PIs and subsequent atherogenesis are well described. [2,39,40] We showed that ART usage had no impact on cIMT in stroke patients. This is likely as a result of the very infrequent use of PI's in our region. The aforementioned meta-analysis from regions

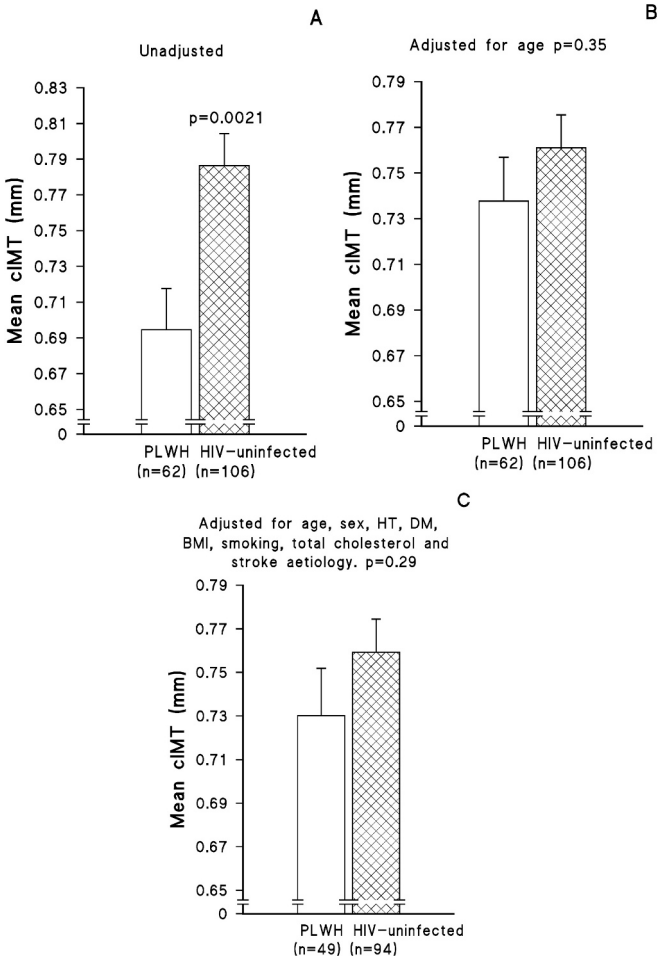

Fig. 2. Bar graphs comparing mean cIMT in PLWH and HIV-uninfected stroke patients with adjustments.
BMI, body mass index; cIMT, carotid intima media thickness; DM, diabetes mellitus; HT, hypertension; PLWH, people living with HIV.

Table 2
Multivariate regression analyses showing determinants of cIMT and increased cIMT.

	Determinants of cIMT (n = 143)		Determinants of increased cIMT (≥0.70 mm) (n = 143)	
Variable	β-coeff. ± SEM	p-value	β-coeff. ± SEM	p-value
HIV status	−0.028 ± 0.027	0.29	−0.844 ± 0.607	0.17
Age	**0.005 ± 0.001**	**<0.0001**	**0.122 ± 0.030**	**<0.0001**
Sex	−0.033 ± 0.029	0.24	0.076 ± 0.660	0.91
HT	**0.076 ± 0.029**	**0.0098**	**2.348 ± 0.631**	**0.0002**
DM	0.033 ± 0.034	0.35	2.287 ± 1.219	0.06
Total cholesterol	**0.035 ± 0.012**	**0.005**	0.393 ± 0.314	0.21
BMI	−0.001 ± 0.002	0.49	−0.012 ± 0.043	0.79
Smoking	0.049 ± 0.035	0.16	0.707 ± 0.856	0.41
Stroke aetiology	−0.004 ± 0.009	0.61	−0.315 ± 0.223	0.16

BMI, body mass index; cIMT, carotid intima media thickness; DM, diabetes mellitus; HT, hypertension. n = 143 (limited by BMI and total cholesterol data).

with higher PI usage also did not report any association between PI usage and cIMT, [4] while a subsequent meta-analysis reported increased cIMT in those on ART and PIs, but only between the ages of 20 and 40 years. [41] Again, the conflicting data illustrates the complexities and uncertainties on the topic.

Stroke in PLWH in SSA is associated with infection in 23–55%. [7] We thus excluded all PLWH with opportunistic infections from our

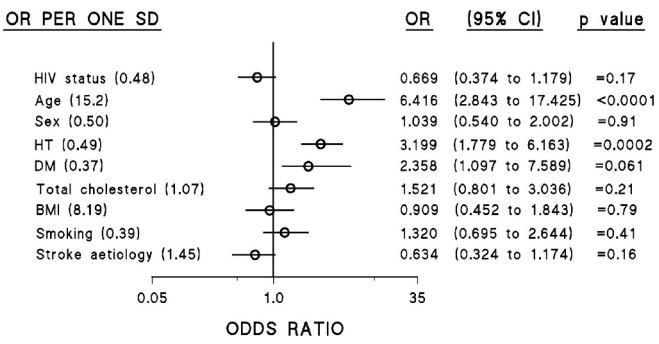

Fig. 3. Determinants of increased cIMT (≥0.70 mm). Odds ratios per one standard deviation of each determinant are shown.

Table 3
Comparing risk factors, cIMT and CD4 in ART-exposed vs ART-naïve PLWH.

	ART-exposed (n = 29)	ART-naïve (n = 33)	p-value
Age (years)	41.9 ± 10.7	43.6 ± 13.5	0.58
Male (%)	48.3	54.6	0.62
HT (%)	34.5	51.5	0.18
DM (%)	0.0	9.1	0.10
Dyslipidaemia (%)	28.6 (n = 28)	30.3 (n = 33)	0.88
Total cholesterol (mmol/L)	4.23 ± 0.92 (n = 28)	3.97 ± 0.91 (n = 33)	0.27
BMI (kg/m^2)	28.1 ± 7.3 (n = 27)	26.7 ± 5.2 (n = 23)	0.44
Smoking (%)	20.7	33.3	0.27
cIMT (mm)	0.67 ± 0.18	0.72 ± 0.18	0.33
CD4 (cells/ul)	385 ± 255	304 ± 190	0.17

BMI, body mass index; cIMT, carotid intima media thickness; DM, diabetes mellitus; HT, hypertension, PLWH, people living with HIV.

Table 4
Determinants of cIMT in PLWH.

	Univariate regression (n = 62[a])		Multivariate regression[b] (n = 59[a])	
Variable	β-coeff. ± SEM	p-value	β-coeff. ± SEM	p-value
Age	**0.008 ± 0.002**	**<0.0001**	**0.005 ± 0.002**	**0.014**
Sex	**−0.098 ± 0.045**	**0.033**	**−0.088 ± 0.043**	**0.045**
HT	**0.140 ± 0.043**	**0.002**	0.061 ± 0.046	0.19
DM	0.088 ± 0.108	0.42		
Total cholesterol (n = 61)	**0.064 ± 0.025**	**0.012**	0.034 ± 0.025	0.17
BMI (n = 50)	0.005 ± 0.004	0.24		
Smoking	0.027 ± 0.052	0.60		
CD4 count (n = 60)	**0.00023 ± 0.00010**	**0.033**	0.00007 ± 0.00009	0.44
ART usage	−0.046 ± 0.046	0.33		

ART, antiretroviral therapy; BMI, body mass index; cIMT, carotid intima media thickness; DM, diabetes mellitus; HT, hypertension, PLWH, people living with HIV.
[a] differences in sample size are due to missing data on total cholesterol (n = 1) and CD4 (n = 2).
[b] including variables with $p < 0.10$ on univariate regression.

cohort, as infection-mediated stroke is unlikely to be related to cIMT, and inclusion of these patients may have resulted in an underestimation of HIV's effect on cIMT. Despite this, our only determinants of cIMT were TRFs. This corroborates with previous non-stroke data from both HICs [3,33,42] and SSA. [29,35,43,44]

It is possible that HIV may confer an increased cardiovascular risk by affecting vessels in a manner which is not detectable on cIMT measurement ie. a non-atherosclerotic vasculopathy. [7,44] If this is indeed

Table 5
Determinants of increased cIMT (≥0.70 mm) in PLWH.

	Univariate regression (n = 62[a])		Multivariate regression[b] (*n* = 47[a])	
Variable	β-coeff. ± SEM	p-value	β-coeff. ± SEM	p-value
Age	**0.026 ± 0.004**	**<0.0001**	**0.017 ± 0.005**	**0.0028**
Sex	−0.171 ± 0.122	0.17		
HT	**0.487 ± 0.108**	**<0.0001**	**0.305 ± 0.122**	**0.017**
DM	**0.678 ± 0.274**	**0.016**	0.381 ± 0.293	0.20
Total cholesterol (*n* = 61)	**0.156 ± 0.066**	**0.021**	0.003 ± 0.066	0.97
BMI (n = 50)	**0.021 ± 0.010**	**0.046**	0.009 ± 0.009	0.35
Smoking	0.078 ± 0.138	0.57		
CD4 count (*n* = 60)	0.00053 ± 0.00027	0.052	−0.00015 ± 0.00025	0.54
ART usage	−0.084 ± 0.123	0.50		

ART, antiretroviral therapy; BMI, body mass index; cIMT, carotid intima media thickness; DM, diabetes mellitus; HT, hypertension, PLWH, people living with HIV.

[a] differences in sample size are due to missing data on total cholesterol (n = 1) and CD4 (n = 2).

[b] including variables with p < 0.10 on univariate regression.

the case, the undisputed value of cIMT in cardiovascular risk prediction may be compromised in our setting, the implications of which would include the need to develop and test alternative risk prediction tools specific to PLWH in SSA. [45,46]

Our findings are likely reflective of the different profile of stroke patients in PLWH in SSA when compared to HICs, with a low atherosclerotic burden despite the exclusion of infections. The aetiology of stroke in our cohort was predominantly non-atherosclerotic, with only 6.5% of PLWH fulfilling the TOAST criteria for large vessel atherosclerotic stroke. It is possible that if we repeated our analyses only in patients with atherosclerotic stroke, the results would differ. Our prevalence of atherosclerotic stroke was too low to perform such analyses.

Besides being the first study to our knowledge to report on the impact of HIV status on cIMT in stroke patients in SSA, other strengths of our study include the use of standardized cIMT measurement methodology which was performed by a single operator, eliminating inter-observer bias, as well as our comprehensive workup for stroke aetiology, and subsequent adjustment for this in the analyses. Limitations included the lack of a non-stroke PLWH group to compare cIMT in PLWH with and without stroke. Our inability to measure BMI in patients unable to stand resulted in some missing data, which may have biased against those with severe strokes in relevant analyses. Selection bias may have played a role as patients were recruited from a quaternary-level hospital, where more atypical stroke patients are more likely to be referred. While we showed no impact of HIV on cIMT in our cohort of stroke patients, our findings may not be generalizable to other populations with a higher atherosclerotic burden. This serves to further highlight the differences in stroke in PLWH between HICs and LMICs and underlines the importance of region-specific research.

5. Conclusion

HIV status had no effect on cIMT in a cohort of stroke patients in a LMIC region with a high prevalence of HIV. The main determinants of cIMT in this cohort were age and hypertension.

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CRediT authorship contribution statement

Eitzaz Sadiq: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Angela Woodiwiss:** Writing – review & editing, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Grace Tade:** Project administration, Methodology, Investigation, Data curation. **Gavin Norton:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Girish Modi:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123186.

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