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Cardioembolic stroke in an HIV endemic region: underdiagnosed and severe

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ABSTRACT

Background and objectives Cardioembolic stroke (CES) appears to be a rare cause of stroke (4%–9%) in people living with HIV (PLWH) in sub-Saharan Africa (SSA). However, due to limited access to diagnostic resources, this may be an underestimate. It is also unclear which cardiac pathologies are the major contributors to CES in this region. We sought to determine the prevalence and aetiology of CES in PLWH and to determine whether there are any differences compared with HIV negative stroke patients.

Methods This cross-sectional study recruited PLWH with new-onset stroke at a quaternary-level hospital in Johannesburg, South Africa, from 2014 to 2017, and compared them to age-matched and sex-matched HIV negative stroke patients. Comprehensive investigations were performed to determine the underlying stroke aetiology, including electrocardiography, echocardiography, CT angiography and cerebrospinal fluid examination.

Results 85 PLWH with ischaemic stroke were recruited and compared with 109 HIV negative controls. CES was identified in 17/85 (20.0%) of PLWH. These patients had more severe strokes than PLWH with non-CES (National Institutes of Health Stroke Scale score 14.9±6.7 vs 11.7±5.4, p=0.04). Cardiomyopathy was the predominant cardiac pathology in PLWH (76.4% vs 45.5% in HIV negative, p=0.04) while valvulopathy was more common in HIV negative patients (42.4% vs 11.8% in PLWH, p=0.03). Arrhythmia (n=1) and ischaemic heart disease (n=1) were uncommon in PLWH.

Conclusion CES is underdiagnosed in SSA and is more severe than non-CES. The identification of cardiomyopathy as the predominant underlying cardiac pathology may assist to target resources towards its detection using accessible cost-effective biomarkers.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cardioembolic stroke (CES) appears to be a rare cause of stroke in people living with HIV (PLWH) in sub-Saharan Africa, although the lack of access to diagnostic resources may be partially responsible for an underestimated prevalence.

WHAT THIS STUDY ADDS

⇒ 20% of strokes in PLWH in this study were due to CES. These strokes were more severe than those with non-CES. HIV-related cardiomyopathy was the most common aetiology.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Resources need to be channelled towards cardiac diagnostics in PLWH with stroke, with a particular emphasis on detecting cardiomyopathy.

INTRODUCTION

Cardioembolic stroke (CES) has been reported to be a relatively rare cause of stroke in people living with HIV (PLWH) in sub-Saharan Africa (SSA), causing only 4%–9% of all strokes.[1 2] However, due to severely limited resources, a comprehensive cardiovascular assessment including echocardiography is seldom possible in stroke patients in this region.[1] It is thus likely that the true prevalence of CES is higher than previously reported.

HIV is associated with cardiac diseases that may predispose to CES, including cardiomyopathy (CM), ischaemic heart disease, valvular heart disease and arrhythmias.[3 4] While the incidence of CM has decreased with antiretroviral therapy (ART),[3] it remains a major cause of morbidity and mortality in regions with poor ART coverage and has been shown to be responsible for up to 38% of cardiac disease in PLWH in SSA.[3 5] The risk of ischaemic heart disease is almost doubled by HIV infection in studies from high-income countries (HICs).[4] However, it appears to be less common in low-middle-income countries (LMICs), with a prevalence of only 2.4% in a large South African study.[5] Valvular heart disease in PLWH in HICs is commonly secondary to intravenous recreational drug use-related infective endocarditis.[6] However, intravenous drug usage is less common in LMICs, with rheumatic heart disease being the predominant cause of valvulopathy in these regions.[7] Finally, CES in PLWH may also be related to cardiac arrhythmia, with an increased prevalence of atrial fibrillation (AF) noted in PLWH in HICs.[8]

Problem statement

Due to a paucity of data from LMICs, it is unclear which cardiac pathologies are largely responsible for CES in PLWH in SSA. Extrapolation of data from HICs may not be appropriate due to the vast differences in ART coverage, patient profiles and cardiac pathologies as described above. In this study, we sought to determine the prevalence and aetiology of CES in PLWH in a LMIC at the epicentre of the world's HIV epidemic and to determine whether there are any differences compared with HIV negative stroke patients.

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 within 48 hours of a new-onset stroke. Stroke was defined as per the WHO case definition.[9] Exclusion criteria were the presence of meningitis on cerebrospinal fluid (CSF) examination (elevated protein, a low serum:CSF glucose ratio or pleocytosis), the presence of intracranial mass lesions on radiographic imaging or other stroke mimics. Full informed consent was obtained as per the Declaration of Helsinki.[10]

All patients were assessed and examined by the same specialist neurologist (ES). Stroke aetiology was classified according to the Trial of Org 10172 in Acute Stroke (TOAST) Classification.[11] Stroke severity was graded according to the National Institutes of Health Stroke Scale (NIHSS).[12]

The cardiac evaluation included a full cardiovascular clinical examination, a 12-lead ECG and transthoracic echocardiography. 24-hour Holter ECG and transoesophageal echocardiography were performed where clinically indicated, particularly in patients with large vessel stroke of undetermined aetiology after standard investigations. These were performed and interpreted by the specialist cardiologist on call, who then assigned the cardiac aetiological category most likely to be responsible for the stroke. The classification of the aetiology of CM was based on the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of Heart Failure.[13] Cardiac wall motion abnormalities due to ischaemic heart disease were categorised separately from CM. Patients with definite cardiac pathology but not meeting the TOAST criteria for CES were categorised as 'Stroke of undetermined aetiology'.

The full protocol of laboratory investigations for underlying stroke aetiology is available in the online supplemental file. HIV testing (ELISA) was performed in all consenting patients. Those found to be HIV positive subsequently had their CD4 count and HIV viral load (VL) measured. A suppressed VL was defined as a VL of less than 50 copies/mL. A lumbar puncture was performed in all PLWH, and those HIV negative were clinically indicated, provided no contraindication was present. CSF was examined as per the protocol in the online supplemental file.

CT scan of the brain was performed in all patients. MRI of the brain and angiography (CT or MRI angiogram) was performed if clinically indicated, particularly if there was no clearly identified cause for the stroke from the preceding investigations, or a vasculitis or vasculopathy was suspected. Angiography included the aortic arch, neck and brain. Carotid stenosis was assessed by means of carotid doppler studies of the distal common carotid artery. All radiological investigations were examined by a specialist radiologist and the same specialist neurologist (ES).

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Statistical methods

Data were analysed by using Statistica V.14.0.0.15, TIBCO Software. Continuous variables were evaluated for normality using Shapiro-Wilk and Kolmogorov-Smirnov tests. χ^2, Fisher's exact test, Student's t-test, Mann-Whitney, Pearson correlation coefficient and Spearman correlation coefficient statistical tests were then performed on parametric and non-parametric variables where appropriate. Continuous data are reported as mean±SD unless otherwise specified. Missing data were not imputed. P values <0.05 were considered significant.

RESULTS

A total of 127 consecutive PLWH with stroke were screened for participation in the study. 40 were excluded due to the presence of abnormal basic CSF findings. As only two PLWH suffered from intracerebral haemorrhage, further analyses were only conducted in ischaemic stroke patients (n=85). These were compared with 109 age-matched and sex-matched HIV negative ischaemic stroke patients, recruited during the same time period.

Aetiology of stroke

When analysed according to HIV serostatus, the relative percentages of cardioembolic, atherosclerotic, small vessel and strokes of undetermined aetiology according to the TOAST criteria were similar in the two groups (table 1). However, the aetiology was classified as 'other' in a higher proportion of PLWH (p<0.001) (table 1). 40/45 (47%) of the PLWH were on ART at the time of stroke.

CES in PLWH

20% of strokes in PLWH (n=17) were due to a cardioembolic cause. (table 1). 76.4% of these (n=13) were secondary to CM (figure 1). The aetiologies of the CM are shown in figure 2 and were mostly secondary to HIV-related dilated CM. Valvular abnormalities were detected in 2 PLWH (both with rheumatic heart disease) while

Table 1 Comparing demographics and stroke aetiology (TOAST criteria) between PLWH and HIV negative patients

	PLWH (n=85)	HIV negative (n=109)	P value
Age (years)	43.4±12.5	45.0±10.5	0.33
Male (%)	49.4	47.7	0.81
TOAST aetiology			
Cardioembolic	17 (20.0%)	33 (30.3%)	0.10
Atherosclerotic	4 (4.7%)	3 (2.8%)	0.47
SVD	14 (16.5%)	20 (18.4%)	0.73
Undetermined	22 (25.9%)	40 (36.7%)	0.10
Other	28* (32.9%)	13† (11.9%)	<0.001

*including vasculopathy (definite and probable, n=26) and stroke due to recreational drug use (n=2).
†including vasculitis (n=6), hypercoagulable state (n=3), neurosyphilis (n=2), stroke due to recreational drug use (n=1) and hyperhomocystinaemia (n=1).
PLWH, people living with HIV; SVD, small vessel disease; TOAST, Trial of Org 10172 in Acute Stroke.

arrhythmia was identified in only 1 PLWH (a patient in their 70s known with a long-standing history of AF). Ischaemic heart disease was the likely source of CES in one PLWH, an ART-naïve patient in their late 50s with multiple traditional cardiovascular risk factors (TRFs). All CES patients were diagnosed as such by transthoracic echocardiography. Transoesophageal echocardiography or 24-hour Holter ECG, where performed, did not diagnose additional cardiac pathology which altered the patient's aetiological classification. None of those with CM had any other significant concomitant cardiac disease on echocardiography.

PLWH with CES (n=17) were compared with PLWH with non-CES (n=68), which revealed a higher stroke severity in those with CES (table 2). Demographics including mean age and proportion of males were similar, as were the prevalences of all TRFs (table 2). HIV-related factors (CD4 count, VL and ART exposure) were also similar between the two groups (table 2).

Univariate and multivariate regression analyses confirmed that the NIHSS score was only influenced by whether the aetiology was CES or non-CES, and not by differences in age, sex or HT status (table 3).

CES in HIV negative patients

In HIV negative patients, 33/109 (30.3%) had CES (table 1). CM (45.5%) and valvulopathy (42.4%) were the most common aetiologies of CES in these patients (figure 1). When compared with PLWH, the relative prevalences of CM and valvulopathy differed significantly (p=0.04 and 0.03 respectively, figure 1). The aetiology of CM in HIV negative patients is shown in figure 2 and contrasted to PLWH.

There was no difference in NIHSS scores between CES and non-CES in HIV negative patients (table 2). The CES patients had a lower mean age and less TRFs (median number of TRFs and obesity) than non-CES (table 2).

Comparison of PLWH and HIV negative patients with CES revealed no difference in demographics, TRFs or stroke severity (table 2).

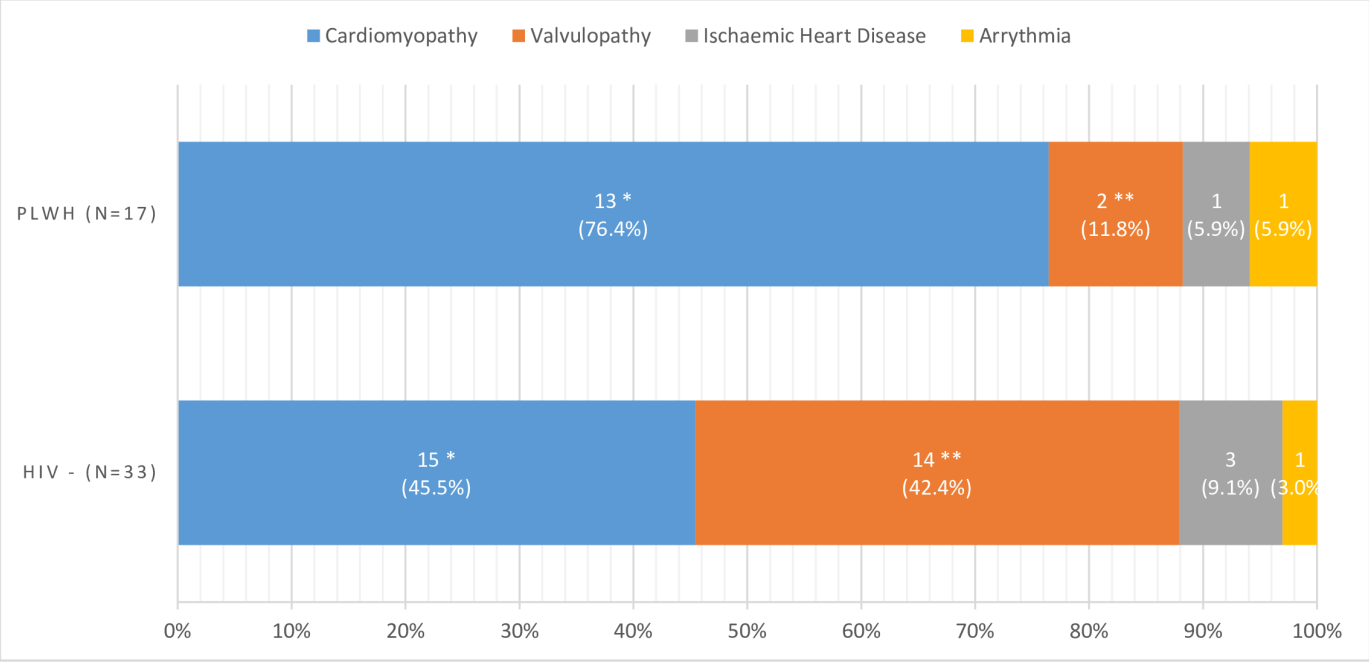

Figure 1 Aetiology of CES in PLWH compared with HIV negative patients. Statistically significant differences are denoted by * or **, where *p=0.04 (CM in PLWH vs HIV negative) and **p=0.03 (valvulopathy in PLWH vs HIV negative). CES, cardioembolic stroke; CM, cardiomyopathy; PLWH, people living with HIV.

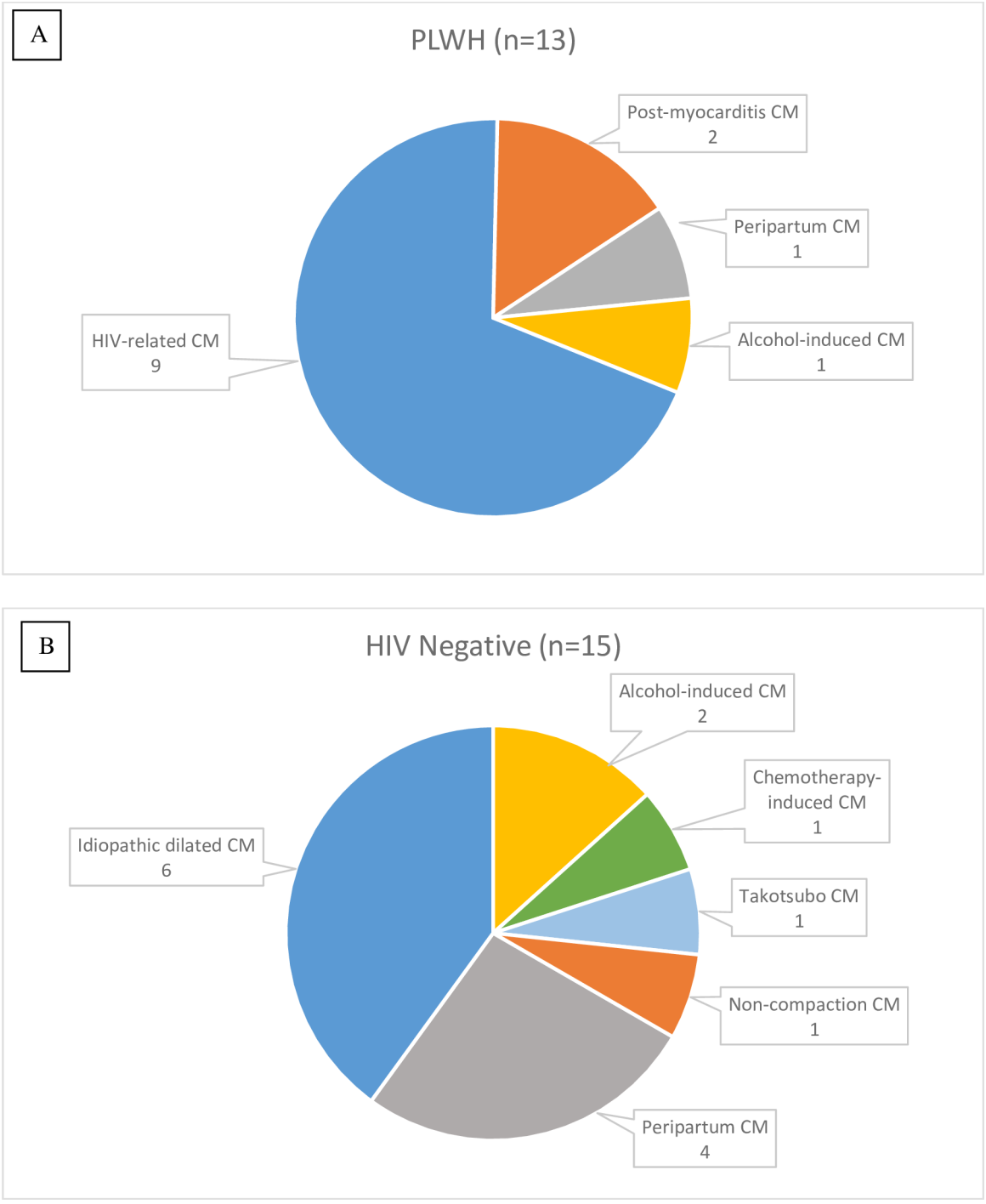

Figure 2 Aetiology of cardiomyopathy (CM) in PLWH (A) and HIV negative (B) patients. PLWH, people living with HIV.

Stroke of undetermined aetiology

Incomplete investigations were the the most common reason for a stroke being classified as being of undetermined aetiology (47/62, 75.8%). There was no difference in the proportion of patients who had incomplete investigations in PLWH compared with HIV negative patients (16/22, 72.7% vs 31/40, 77.5%, p=0.55). Transthoracic echocardiography was not possible in only two patients while transoesophageal echocardiography (n=15) and 24-hour Holter ECG (n=8) were not possible in a larger number of patients. Six patients demised prior to their full workup being completed. 19/22 PLWH with strokes of undetermined aetiology had large vessel strokes, of which 6 had prominent cardiac pathology but was insufficient to categorise them as CES as per the TOAST criteria.

Stroke severity

The mean NIHSS score did not differ between HIV negative and PLWH stroke patients overall (12.0±5.9 vs 12.4±5.8, p=0.68). Besides the higher stroke severity in PLWH with CES as described above, there were no

Table 2 Comparing CES to non-CES in PLWH and HIV negative patients and comparing CES in PLWH to HIV negative patients

	PLWH (n=85)			HIV negative (n=109)			P value (CES in PLWH vs CES in HIV negative)
	CES (n=17)	Non-CES (n=68)	P value	CES (n=33)	Non-CES (n=76)	P value	
Age (years)	43.6±14.3	43.3±12.1	0.93	41.8±10.4	46.3±10.3	0.04	0.63
Male (%)	64.7	45.6	0.16	48.5	47.4	0.91	0.27
HT (%)	41.2	44.2	0.83	48.5	65.8	0.09	0.62
DM (%)	5.9	5.9	1.00	12.1	27.6	0.08	0.49
Dyslipidaemia (%)	23.5	25.0	0.90	24.2	32.9	0.37	0.96
Smoking (%)	23.5	26.5	0.80	15.2	19.7	0.57	0.47
Obesity (%)	23.1 (3/13)	26.5 (13/49)	0.80	19.2 (5/26)	41.9 (23/55)	0.046	0.78
Median no of TRFs (IQR)	1 (1–2)	1 (0–2)	0.77	1 (0–2)	2 (1-3)	0.01	1.00
NIHSS	14.9±6.7	11.7±5.4	0.04	11.9±6.7	12.1±5.6	0.87	0.15
CD4 (cells/µL)	353.2±157.6	318.4±220.1 (n=64)	0.54				
Median VL (IQR) (copies/ml)	1600 (0–131 540)	2200 (0–67 264)	0.77				
ART-exposed (%)	47.1	47.1	1.00				
Suppressed VL (%)	85.7	65.6	0.30				

.ART, antiretroviral therapy; CES, cardioembolic stroke; DM, diabetes mellitus; HT, hypertension; NIHSS, National Institute of Health Stroke Scale; PLWH, people living with HIV; VL, viral load.

other differences in stroke severity between the other aetiological categories in PLWH (data are available on request). In PLWH, there was no correlation between CD4 count and NIHSS (r=−0.141, p=0.90, n=81) or VL and NIHSS (r_s=−0.098, p=0.41, n=72). There was also no difference in NIHSS between those exposed to ART or not, or those with a suppressed VL or not (data are available on request).

DISCUSSION

Our cohort of 85 PLWH with ischaemic stroke is one of the largest from SSA and one of the most extensively investigated.[1 2] We showed that 20% of strokes in PLWH were of cardioembolic origin, of which 76.4% were secondary to CM. PLWH with CES suffered from more severe strokes than PLWH with non-CES.

Our prevalence of CES is higher than other PLWH cohorts in SSA and other LMICs (4%–9%).[1 2] However, less than 60% of the participants in these studies had an ECG or echocardiography, compared with the detailed cardiac assessments performed in our cohort. Our higher prevalence of CES thus likely illustrates the desperate need for improved access to resources in order to adequately diagnose CES.

Table 3 Risk factors (RF) associated with NIHSS in PLWH on univariate and multivariate regression analyses

Univariate regression (n=85)			Multivariate regression* (n=85)	
RF	β-coefficient±SEM	P value	β-coefficient±SEM	P value
Age	−0.0263±0.0512	0.61	0.008±0.054	0.88
Sex	0.7686±1.2714	0.55	1.131±1.276	0.35
Smoking	−1.810±1.441	0.21		
HT	−2.040±1.265	0.11	−1.949±1.323	0.14
DM	0.488±2.707	0.86		
Dyslipidaemia	−1.844±1.463	0.21		
Obesity	−0.226±1.682	0.89		
CD4 (n=81)	−0.001±0.003	0.90		
VL (n=72)	−0.001±0.001	0.83		
ART exposure	1.103±1.271	0.39		
VL suppression (n=39)	0.592±1.951	0.76		
Non-CES vs CES	**−3.221±1.544**	**0.04**	**−3.390±1.560**	**0.03**

*Age, sex and only those RF where p≤0.20 on univariate analyses were included in the multivariate analysis. Significant RFs are shown in bold type.
ART, antiretroviral therapy; CES, cardioembolic stroke; DM, diabetes mellitus; HT, hypertension; PLWH, people living with HIV; RF, risk factor; VL, viral load.

Previous SSA data on CES is very limited but does not appear to show any significant difference in the type of cardiac abnormalities when comparing PLWH to HIV negative CES patients.[2 14–16] We found CM to be the most common pathology in PLWH while valvulopathy was more common in HIV negative patients. A study from a similar population to ours reported CM in six out of nine PLWH with CES but did not compare these to HIV negative patients.[14] If it is indeed true that the source of CES in our PLWH population is more likely to be CM, this has the potential to guide a targeted search for the most likely sources of CES in a particular population. Our very low prevalence of arrhythmia (1 out of 17 PLWH with CES) adds further value to this model. We did not detect any further patients to have arrhythmia despite the use of 24-hour Holter ECG in most patients. This suggests that such resources may be better allocated towards detecting cardiac abnormalities such as CM, as opposed to an intensive search for arrhythmia in this stroke population. In regions such as SSA, the rational allocation of scarce diagnostic resources is of great importance.

A recent consensus paper presented an insightful diagnostic algorithm and defined the minimum set of recommended investigations for determining the aetiology of a stroke in PLWH.[17] This included an ECG and transthoracic echocardiography as a minimum. Unfortunately, echocardiography in particular is an extremely scarce resource in SSA. It requires not only equipment, but more importantly, the technical expertise to perform and interpret the examination. Due to massive economic and healthcare system challenges, it is very unlikely that widespread access to echocardiography is a realistic solution to diagnosing CES in populations such as ours, with a high HIV burden. The use of alternative cost-effective biomarkers for CES which are more readily accessible and requiring less technical expertise may be the more practical solution.[18 19] In order to guide the development and testing of these biomarkers, it is important to know which particular cardiac diseases are most prevalent in a particular stroke population, which appears to be CM in our PLWH population.

The clinical implication of a missed cardioembolic source is profound, as these patients are at very high risk of recurrent strokes if not treated with the appropriate anticoagulation. Data from AF studies have shown a greater than 70% reduction in recurrent CES using this strategy.[20] In the case of CM (or other causes of heart failure with reduced ejection fraction), there is also good evidence for stroke risk reduction with anticoagulation when used in the correct circumstances, particularly in those patients with a previous thromboembolic event of no alternative aetiology.[21] This applies to a large proportion of the CES patients we have described. The missed opportunity to anticoagulate such patients may lead to recurrent strokes, with their associated additive morbidity and mortality.

Our findings of CES being more severe than non-CES in PLWH are alarming. CES stroke unrelated to HIV infection has been shown to cause more severe stroke in large HIC studies.[22] However, the majority of these strokes are in older patients with AF and multiple other TRFs.[23] This is a vastly different patient profile to our description, emphasising the novelty of our findings. To our knowledge, there have been no previous data examining the differences in stroke severity between different stroke aetiologies in PLWH in our region. We did not detect any difference in stroke severity in HIV negative CES patients when compared with non-CES, nor was there any significant difference in stroke severity across the other aetiological categories. It remains unclear what predisposes PLWH with CES to having more severe strokes and warrants further investigation. We did not detect a difference in stroke severity between PLWH and HIV negative stroke patients in keeping with most previous SSA studies reporting on stroke severity.[1 24–26]

Limitations

The TOAST classification has limitations for classifying ischaemic stroke in a young PLWH population. Previous studies have shown a large proportion of patients falling into the 'undetermined' or 'other' categories due to alternative stroke aetiologies.[17] Despite this, we chose to categorise according to this classification, to allow comparison with previous data. The consensus paper on aetiological classification of stroke in PLWH also agreed with criteria very similar to those in TOAST to diagnose CES in PLWH.[17] We acknowledge that our exclusion of patients with meningitis may have resulted in a greater relative proportion of CES. We re-examined the published data from the five SSA studies which described the relative percentages of CES and stroke associated with infectious aetiology.[1 14 15 24 27 28] After exclusion of the latter, the percentage of CES still ranged from 4% to 12%. The only exception was Tipping *et al*, where the relative contribution of CES rose to 21% once infections were excluded.[14]

While our overall prevalence of stroke of undetermined aetiology was within the international norm of approximately one-third of all strokes,[29] a large proportion of these were due to incomplete investigations. We describe a very low prevalence of arrhythmia; however, we could not perform a 24-hour Holter ECG in eight patients with stroke of undetermined aetiology, nor did we have access to any prolonged cardiac rhythm monitoring beyond 24 hours. Thus, it is possible that paroxysmal arrhythmia may have gone undetected in some of these patients. Similarly, transoesophageal echocardiography was not possible in 15 patients. While this missing data may have altered our reported aetiologies of CES, they also serve to illustrate that our reported prevalence of CES is also likely to be an underestimate.

CONCLUSION

With a detailed cardiac assessment, we found CES to be the likely stroke mechanism in 20% of strokes in PLWH, which is almost double that which has been previously

reported in SSA. The most common underlying cardiac pathology differed significantly between PLWH (CM) and HIV negative (valvulopathy). Alarmingly, we have shown PLWH with CES to have more severe strokes than those with non-cardioembolic aetiology. This, together with the intrinsically higher stroke recurrence risk in untreated CES, points to an urgent need to address the probable underdiagnosis of CES as a cause of stroke in PLWH in SSA.

Contributors ES: conception and design, data acquisition, data analysis, data interpretation, writing. AW: conception and design, data analysis, data interpretation, review and editing. GN: conception and design, data interpretation, review and editing. GM: conception and design, data interpretation, review and editing. ES is responsible for the overall content as guarantor.

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Patient consent for publication Not applicable.

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