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Stroke and HIV in Botswana: A prospective study of risk factors and outcomes

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ABSTRACT

Objective: HIV is associated with an increased risk of stroke, but there are sparse data on risk factors for stroke in people living with HIV in Sub-Saharan African. The goal of this study was to identify HIV-specific stroke characteristics and risk factors among adults in Botswana.

Methods: We conducted a prospective cohort study in Gaborone, Botswana from June 2015 to June 2017 comparing risk factors and outcomes among adults with and without HIV admitted for acute stroke. In addition, we conducted a case-control study comparing patients with HIV and stroke to outpatients with HIV and no history of stroke.

Results: A total of 52 patients with imaging-confirmed acute stroke were enrolled. Stroke patients with HIV were younger than those without HIV (median age 40 vs 54, $p = .005$). Hypertension was the most common risk factor identified in both HIV+ and HIV- groups, but was more common in patients without HIV (81% vs. 55%, $p = .04$). Patients with HIV were significantly more likely to have a small-vessel lacunar syndrome compared to patients without HIV (67% vs. 29%, $p = .02$). In the case-control analysis, patients with HIV and stroke were more likely to have hypertension than stroke-free controls (53% vs. 16%; OR 7.2, 95% CI 1.5–33.8, $p = .01$), and were more likely to drink alcohol (53% vs. 21%, OR 3.7, 95% CI 1.1–12.1, $p = .03$).

Conclusions: Individuals with HIV present with strokes at younger ages than individuals without HIV. Among those with HIV, hypertension and alcohol use are significant risk factors for stroke.

1. Introduction

Stroke is responsible for approximately 10% of total deaths worldwide and is an increasingly common cause of death in Sub-Saharan Africa [1,2]. HIV is associated with an increased risk of stroke, particularly in young people, and the HIV epidemic in Sub-Saharan Africa has further increased the incidence of stroke in this region [2–4]. The widespread use of antiretroviral therapy (ART) has transformed the HIV epidemic from a nearly universally fatal illness into a chronic, manageable condition for many people living with HIV (PLWH) [4–6]. Chronic complications from HIV such as cardiovascular and cerebrovascular disease now account for a comparatively greater proportion of HIV-associated morbidity and mortality as opportunistic infections have become less common [7].

HIV infection may be associated with stroke through several different mechanisms including opportunistic infections, vasculopathy, hypercoagulability and metabolic effects of antiretroviral drugs, such as protease inhibitor induced hypercholesterolemia [1–6]. However, there are little published data on stroke in patients with HIV in Sub-Saharan Africa, where most PLWH reside [2,3]. Many prior studies of HIV and stroke have been limited by lack of imaging confirmation of stroke and lack of an appropriate HIV positive, stroke-free control group [2,3]. As a result, risk factors for stroke in PLWH in Sub-Saharan Africa have not been well defined. This knowledge gap precludes the development of effective prevention strategies.

Botswana is a Sub-Saharan nation with a very high HIV prevalence [7,8]. More than two-thirds of PLWH in Botswana are treated with ART, making this an ideal population in which to study chronic

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complications of HIV [9]. The goals of the current study were two-fold. First, we aimed to describe stroke type, risk factors, and outcomes in a prospective cohort of stroke patients with and without HIV admitted to Princess Marina Hospital in Botswana. We hypothesized that PLWH and stroke, when compared to HIV-uninfected patients with stroke, would be younger and have fewer conventional risk factors such as hypertension and diabetes. We also hypothesized that outcomes including mortality and modified Rankin scale at follow up would be poorer among PLWH. Second, we aimed, to conduct a nested case-control study comparing PLWH with stroke to age-matched PLWH but no history of stroke. We hypothesized that PLWH and stroke would have more advanced WHO stage and lower CD4 count nadir.

2. Methods

2.1. Study design

We conducted a prospective cohort study at Princess Marina Hospital in Gaborone, Botswana from June 2015 to June 2017 and compared PLWH admitted for acute stroke to patients without HIV admitted for acute stroke. In addition, we conducted a case-control study comparing PLWH with stroke to age-matched controls (PLWH with no history of stroke; See Fig. 1).

2.2. Study setting

Patients with acute stroke were recruited from inpatient medical wards at Princess Marina Hospital (PMH) in Gaborone, Botswana. Age-matched control PLWH and no history of stroke were recruited from the outpatient HIV clinic at Princess Marina Hospital (PMH). PMH is a tertiary national referral hospital and a teaching hospital for the University of Botswana with approximately 560 beds. The patient population is a combination of self-referrals from areas within Gaborone, and referrals from primary health care units and district hospitals for specialized or higher-level care. A Computed Tomography (CT) scanner located at the hospital is routinely used for patients with suspected stroke. Magnetic Resonance Imaging (MRI) is available at an outpatient private radiology facility, but is not routinely available for patients admitted to PMH.

Acute stroke was defined by a clinical presentation withrapidly developed clinical signs of focal disturbance of cerebral function lasting more than 24 h and presumed to be due to a vascular origin, with neuroimaging consistent with a diagnosis of stroke. Patients with both ischemic stroke and intraparenchymal hemorrhage were included. Transient ischemic attacks (symptom duration < 24 h) were excluded, as were subdural, epidural, intraventricular, or subarachnoid hemorrhage without parenchymal hemorrhage. Subjects who had a prior history of stroke, but who did not have new focal deficits at the time of presentation, were not included.

Inclusion criteria include: 1) age ≥ 18 years, 2) diagnosis of acute stroke suspected by the clinical team caring for the patient, 3) evidence of a focal neurologic process by history or physical examination, and 4) neuro-imaging with either CT scan or MRI. *Exclusion criteria include:* 1) known CNS tumor or metastatic disease, 2) altered mental status and/or coma as the presenting symptoms, without evidence of a focal process by history, physical examination, or neuro-imaging, 3) seizure activity without other, non-epileptic, focal deficits 4) stroke occurring secondary to surgery, poisoning, or major traumatic injury, 5) Symptom duration < 24 h, 6) Subdural, epidural, and/or subarachnoid hemorrhage without parenchymal hemorrhage 7) Neuroimaging suggestive of an alternate diagnosis other than acute stroke 8) Evidence of central nervous system infection with an organism other than HIV.

2.3. Process of recruitment

A study research nurse or study physician surveyed all newly-admitted patients to Princess Marina Hospital to identify eligible patients daily on weekdays. All patients with suspected stroke were reviewed by a study nurse to determine if they met inclusion/exclusion criteria. Eligible patients, or their legally authorized representative, were approached to obtain informed consent.

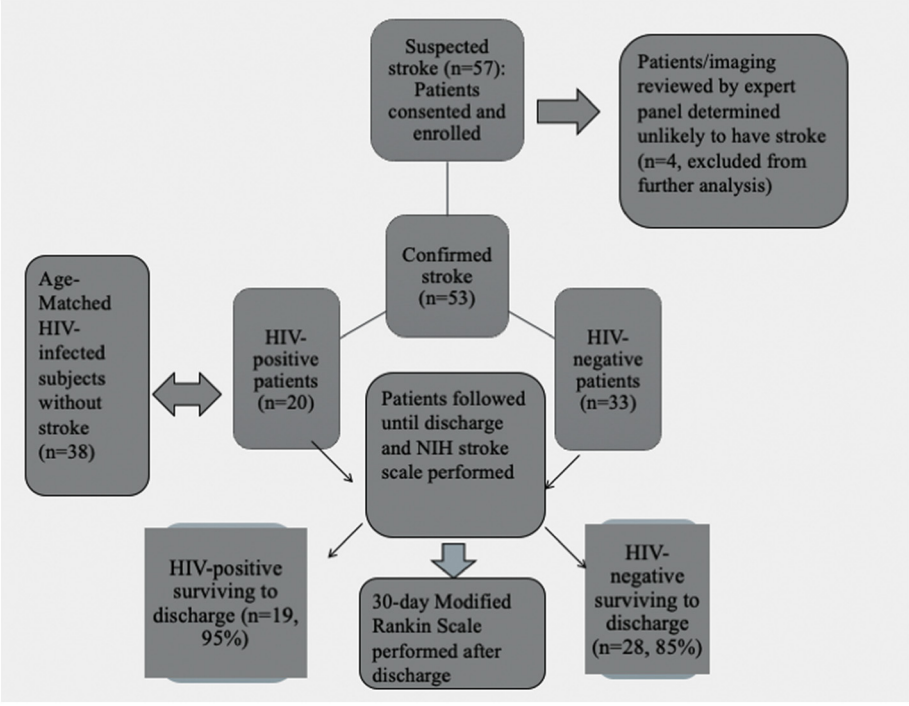

Fig. 1.. Flow chart of study design and enrollment, stratified by HIV Status.

2.4. Data collected

Data on key variables was collected based on an adapted version of the World Health Organization "STEPwise Approach to Stroke Surveillance" questionnaire [10]. Data were obtained from a combination of medical record review, interview with the medical team, and direct interview of the patient and/or their caregiver. Data collected included demographics, past medical history, HIV history, and National Institute of Health Stroke Scale (NIHSS) [11] at admission and discharge. History of hypertension, diabetes, and prior stroke was abstracted from the patient's medical record and confirmed where possible through patient or caregiver interview. Alcohol and smoking history was ascertained through patient and/or caregiver interview. Height, weight, and mid-upper arm circumference were measured by a study nurse. Results of labs performed during routine clinical care were recorded, including complete blood count, basic metabolic panel, lipid panel, random or fasting capillary blood glucose, rapid plasma reagent for syphilis, CD4 count, viral load, and CSF analysis if performed. Results of diagnostic testing performed during routine clinical care were recorded, including EKG, echocardiogram, brain and cerebrovascular imaging. A follow-up visit was conducted either in person or by phone 30–90 days post stroke and outcomes including mortality and Modified Rankin Scale (mRS) [12] were assessed. All NIHSS and mRS were assessed by a trained rater, certified in the use of these scales [11,13,14].

2.5. Classification of stroke

All brain imaging was interpreted by a radiologist (SS). Classification of stroke type and subtype was done independently by two study investigators (MM, DB, both neurologists) blinded to HIV status after reviewing the clinical history and imaging. Classification was adjudicated by a third neurologist (SK) when there was disagreement among the first two reviewers. First, a diagnosis of stroke was confirmed. For all confirmed stroke cases, the clinical subtype of stroke (ischemic or intracerebral hemorrhage) was recorded. For ischemic stroke, cases were further classified using two different classification schemes - the Bamford classification, which describes clinical stroke syndromes and divides ischemic stroke into: lacunar, partial anterior circulation syndrome, complete anterior circulation syndrome, and posterior circulation syndrome; and the TOAST criteria which divides ischemic stroke by presumed etiology: large artery atherosclerosis, cardioembolism, small artery occlusion, stroke of other determined cause, cryptogenic despite adequate evaluation, and insufficient information to make a determination [15,16].

2.6. Identification of control patients for case-control analysis

For each patient with HIV and stroke, two age-matched patients with HIV and no clinical history of stroke or TIA were prospectively recruited from the outpatient HIV clinic at Princess Marina Hospital for a 2:1 matched case control analysis. Matched patients were required to be +/− 5 years in age of the case to which they were matched, and the first eligible patients meeting matching criteria were approached for consent and enrollment..

2.7. Statistical analysis

Variables were summarized by means and standard deviations or medians and interquartile ranges for continuous variables, and frequencies/proportions for categorical variables overall, and stratified by HIV status. Differences between HIV-infected and HIV-uninfected groups were evaluated using chi-squared or exact tests for categorical variables, and *t*-tests or log-rank tests for continuous variables. In the case-control study, differences between groups were initially evaluated using univariate conditional logistic regression. All variables that were significant in the univariate analysis at a level of $p \leq .25$ were evaluated in a multivariable conditional logistic regression or standard logistic regression model using a manual stepwise backward selection procedure. Missing data were addressed with pairwise deletion. *A sample size of 51 stroke cases among PLWH was initially planned in order to have 80% power to detect odds ratios of 3.0 or greater in the case control analysis.*

2.8. Ethics statement

This study was reviewed by all relevant IRBs, including IRBs at the Botswana Ministry of Health, University of Botswana, Princess Marina Hospital, and the University of Pennsylvania. Verbal and/or written informed consent was provided by all patients or patients' legally authorized representatives in those patients who were unable to consent for themselves due to their neurologic injury.

3. Results

3.1. Characteristics of patients with stroke

Over the period of the study, a total of 147 patients with suspected stroke presented to the hospital. Of these, we enrolled a total of 57 patients (39% of total) with suspected stroke, of whom 52 had confirmed stroke after adjudication (see Fig. 1). 12 patients did not consent to participation, and 78 patients with suspected stroke either died or were discharged before they could complete the consent process. All patients with confirmed stroke had imaging with computed tomography; 3 patients also had magnetic resonance imaging. 36 patients had ischemic strokes while 16 had intracerebral hemorrhage. Of these 52 patients, 20 (38%) had HIV, while 32 (62%) did not. Demographics and risk factors in each group are detailed in Table 1. Patients with HIV and stroke were significantly younger than patients without HIV (median age 40 vs 54, $p = .005$). Hypertension was the most common risk factor identified in both PLWH and HIV-negative groups, but was more common in HIV-negative patients (81% vs. 55%, $p = .04$). History of previous stroke was common in both groups (25% vs 22%, $p = 1.0$). Other risk factors such as diabetes, hypercholesterolemia, and atrial fibrillation, were uncommon in both groups. Of these 52 patients with stroke, 8% reported never having a blood pressure checked prior to their stroke admission, 40% reported never having been screened for diabetes prior to their admission and 98% reported never having been screened for hyperlipidemia prior to their admission. Of the 36 ischemic strokes, 78% received aspirin on the day of admission, and 63% received a statin at the time of hospital discharge. DVT prophylaxis was started within 1 day of admission in 42% of ischemic strokes and 65% of stroke patients saw physical therapy during their hospitalization.

3.2. Stroke type and subtype (see Table 2)

Among the HIV positive stroke cases, 75% were ischemic stroke and 25% were ICH. In patients without HIV, 66% had ischemic stroke and 34% had ICH. Stroke type was not significantly different between patients with and without HIV. All of the ischemic strokes were classified according to the Bamford classification. Patients with HIV were significantly more likely to have a lacunar syndrome (67% vs. 29%, $p = .02$). Patients without HIV were numerically more likely to have a partial anterior circulation syndrome although this did not reach statistical significance (57% vs. 27%, $p = .07$). When classifying stroke etiology according to TOAST classification, there was an insufficient evaluation to make a determination in 61% of all patients. An etiology was identified in 53% of patients with HIV and 29% of patients without HIV. The most common identified etiologies in PLWH were cardioembolism (in 27%) and small vessel disease (in 27%), while the most common identified etiology in HIV-negative patients was cardioembolism (in 14%). Vascular imaging (for example, with carotid ultrasound or CT angiography) was not performed in most subjects, and thus it was

Table 1
Demographic characteristics and risk profiles of study participants at admission stratified by HIV status.

Characteristics	Overall (n = 52)	HIV-Negative (n = 32)	PLWH (n = 20)	P-value
Median age (IQR)	48 (36–66)	54 (41–74)	40 (34–48)	< 0.01*
Female sex	29 (56%)	16(50%)	13(65%)	0.29
Education - n (%) having completed secondary school or higher	25 (48%)	13 (41%)	12 (60%)	0.17
Past medical history				
Hypertension	37 (71%)	26 (81%)	11 (55%)	0.04*
Diabetes	2(4%)	1(3%)	1(5%)	1.00
Prior stroke	12(23%)	7(22%)	5(25%)	1.00
Current smoker	15 (29%)	10(31%)	5(25%)	0.76
Alcohol intake in the past 12 months	21(40%)	11(34%)	10(50%)	0.26
Nutritional status				
Body mass index, median (IQR)	26.7 (23.3–31.8)	26.3 (23.6–32.2)	27.3 (22.8–30.8)	0.74
Median mid-upper arm circumference, in inches (IQR)	11 (10 – 13)	11 (10–13)	11 (10 – 12)	0.43
Median waist circumference, in inches (IQR)	36 (30–42)	34 (30–40)	38(33–44)	0.13
Stroke details				
Median NIHSS at admission (IQR)	10 (6–19)	9 (5–23)	11 (7–14)	0.76
Median GCS at admission (IQR)	15 (12–15)	15 (11–15)	15 (15–15)	0.10
Stroke subtype				0.55
Ischemic stroke	36 (68%)	21 (64%)	15 (75%)	
ICH	16 (30%)	11 (33%)	5 (25%)	

GCS = Glasgow Coma Scale; ICH = Intracerebral hemorrhage; IQR = Interquartile range; NIHSS = National Institute of Health Stroke Scale; PLWH = People Living with HIV; TIA = Transient Ischemic Attack.
* Designates p-value of ≤0.05.

not possible to accurately assess the contribution of large artery atherosclerosis.

3.3. Stroke severity and outcomes

There was no difference in stroke severity between patients with and without HIV as measured by the NIH Stroke Scale (median 10.5 vs. 9, p = .76). There were also no significant differences in mortality (15.6% vs. 5%, p = .39). Follow-up outcome assessment occurred in 84.8% of patients that survived to hospital discharge (79.0% of patients with HIV and 84.8% of patients without HIV). There was no significant difference in Modified Rankin Score at follow up between groups (median 3 vs. 2, p = .48) and no patients reported recurrent stroke during the period of follow up.

3.4. Case-control analysis (see Table 3)

Characteristics of patients with HIV and stroke (cases) compared to HIV-infected patients with no history of stroke (controls) are described in Table 3. For one patient with HIV and stroke, no control patients could be identified due to the patient's advanced age, leaving a total of 19 analyzable patients with HIV and stroke and 38 control patients with HIV and no history of stroke. Cases and controls were demographically similar, with no differences noted in age, sex, or level of education. Cases were significantly more likely to have hypertension than controls (53% vs. 16%; OR 7.2, 95% CI 1.5–33.8, p = .01), and were significantly more likely to drink alcohol (53% vs. 21%, OR 3.7, 95% CI 1.1–12.1, p-0.03). Smoking was more common in cases, but this did not reach the threshold for statistical significance (26% vs. 5%, OR 8.6, 95% CI 1.0–74.9, p = .05). Controls were more likely than cases to be taking antiretroviral therapy (100% vs. 73%, p < .001; OR not calculated due to perfect prediction) and had been treated with ART for a longer period (mean time on treatment 9.0 years vs 5.7 years, p = .04). Controls were also more likely to have had a viral load below the limit of detection of 400 copies/ml (92% vs. 26%, OR = 0.03, 95% CI 0.01–0.15, p ≤.001; OR calculated using standard logistic regression due to small number of patients). Viral load had not been performed or was missing in a large proportion of cases with HIV and stroke (68%), primarily due to the fact that many stroke patients were either not on ART or had only been started on ART recently and viral load had not yet been measured. Efavirenz-based antiretroviral drug (ART) regimens were the most common regimens utilized, with no differences in use between cases and controls (45% vs. 42%, p = .8) Protease inhibitors were used in only 4 patients (in 1 case and 3 controls). Cases had been more recently diagnosed with HIV than controls (median time since diagnosis 1 year vs. 11 years, p = .004). In a multivariable conditional logistic regression model controlling for age, sex, smoking, and alcohol use, hypertension remained strongly associated with stroke (OR 9.0; 95% CI 1.5–54.4; p = .02). HIV-specific variables were not able to be included in the multivariable model as small numbers of patients in each cell led to model instability. However, including HIV-specific variables in standard logistic regression models along with hypertension did not significantly change the association between hypertension and stroke.

4. Discussion

In this study, we investigated the relationship between HIV and

Table 2
Ischemic stroke type according to bamford classification.

	Overall (n = 36)	HIV-negative (n = 21)	PLWH (n = 15)	P-value
Bamford Classification				
Lacunar	16 (44%)	6 (29%)	10 (67%)	0.02*
Partial anterior circulation syndrome	16 (44%)	12 (57%)	4 (27%)	0.07
Complete anterior circulation syndrome	3 (8%)	2 (10%)	1 (7%)	0.76
Posterior circulation syndrome	1 (3%)	1 (5%)	0	0.73

* Designates p-value of ≤0.05.

Table 3
Characteristics of PLWH with Stroke (Cases) vs. PLWH without Stroke (Controls).

Characteristics	Controls (n = 38)	Cases (n = 19)	Odds Ratio	95% CI	P-value
Age, median (IQR)	39 (37–45)	39 (34–47)	1.01	0.77–1.34	0.92
Female Sex	30(79%)	12(63%)	2.27	0.63–8.19	0.21
Completed secondary school	26(68%)	12(63%)	0.76	0.22–2.67	0.67
Hypertension	6(16%)	10(52%)	7.19	1.53–33.81	0.01*
Diabetes	1(3%)	1(5%)	2.00	0.13–31.98	0.62
Current smoker	2(5%)	5(26%)	8.58	0.98–74.91	0.05
Alcohol intake in the past 12 months	8(21%)	10(53%)	3.68	1.12–12.12	0.03*
Body Habitus					
Body mass index, median (IQR)	24.8 (21.5–30.5)	27.2 (22.6–30.5)	1.02	0.92–1.14	0.67
Waist circumference, inches, median (IQR)	34 (32–38)	38 (33–44)	1.08	0.98–1.19	0.12
HIV history					
Time since HIV diagnosis, years	11 (9–12)	1 (0–8)	0.77	0.64–0.92	< 0.01*
Current CD4, median (IQR)	656 (433–747)	556 (400–755)	1.00	1.00–1.00	0.55
Nadir CD4, median (IQR)	159 (67–190)	240 (108–400)	1.01	1.00–1.01	0.18
WHO Stage					0.15
Stage 1	33(87%)	15(79%)			
Stage 2	1(3%)	0			
Stage 3	1(3%)	0			
Stage 4	0	2(11%)			
Missing	3(8%)	2(11%)			
Last Viral Load					
≤400 copies/ml	35(92%)	5(26%)	0.03 0.01–0.15		< 0.001*
401–999 copies/ml	0	0			
≥1000 copies/ml	2(5%)	1(5%)			
Not performed/missing	1(3%)	13(68%)			
Line of ARV Therapy					
Not on treatment	0	7(37%)			
1st Line	34(90%)	9(47%)			
2nd Line	4(11%)	0			
Missing	0	3(16%)			

PLWH, People Living with HIV; IQR, Interquartile Range; ARV, Antiretroviral; WHO, World Health Organization *Designates p-value of < 0.05.

stroke in patients admitted to a tertiary care hospital in Gaborone, Botswana. The primary objectives of this study were to characterize differences in stroke type, risk factors, and outcomes between PLWH and people without HIV.

4.1. Stroke type

Key findings from this study are that PLWH have an increased risk of lacunar stroke syndromes. This difference in stroke type was not driven by conventional risk factors for lacunar strokes. Stroke etiology must be interpreted with caution in our cohort because many patients did not have a sufficient evaluation to determine an etiology; for example, in the absence of vascular imaging, assigning an etiology according to TOAST criteria is likely to be unreliable. However, the Bamford classification, which characterizes strokes based on clinical presentation, was assessed in all subjects.

4.2. Risk factors

Hypertension was identified as a key risk factor for stroke in both PLWH and in patients without HIV. Patients who presented with stroke had been diagnosed with HIV more recently than HIV-infected controls without stroke, and were less likely to be receiving ART and to be virally suppressed. We did not identify any differences in ART regimens between patients with stroke and controls, although it is notable that very few patients in this study were treated with protease inhibitors, and most patients with HIV and stroke had a very short period of ART exposure.

Outcomes: Contrary to our hypothesis, there were no significant differences in outcomes between PLWH and HIV-negative patients with stroke, although small numbers may have limited our power to detect differences. Prior studies of HIV and stroke are conflicted, with some describing worse outcomes in patients with HIV and others showing no difference [28,29,43,44]. Relatively better outcomes in the patients with HIV in our study compared to those studies may be related to the fact that we excluded patients with central nervous system opportunistic infections, or may have been driven by the younger age of PLWH and stroke, relative to HIV-negative strokes, in our study.

Strengths of the current study include a well-characterized population and confirmation of stroke and stroke subtypes by two independent neurologists. This study contributes to the growing body of literature suggesting that HIV predisposes younger patients to have strokes. The mechanism for stroke in PLWH is likely to be partially related to traditional vascular risk factors, given the increased rates of hypertension, tobacco, and alcohol use in cases, relative to PLWH without stroke. These findings are consistent with other studies which have shown an increased risk of small vessel disease in HIV-infected individuals [1–5,17–19]. Whether this is secondary to premature atherosclerosis, other HIV-associated vasculopathy, or some other mechanism is unclear. Multiple studies have shown an association between traditional vascular risk factors and stroke risk in PLWH, although studies specific to Sub-Saharan Africa have been variable, with some studies identifying relatively high rates of conventional risk factors such as hypertension, diabetes, and hypercholesterolemia, and other studies finding few such factors [2,3,20–29]. It is likely that a key determinant is the overall health of the HIV-infected population studied as well as the proportion that are effectively treated with ART. In addition, the extent to which patients with HIV are screened and treated for conventional risk factors such as hypertension may vary widely between countries. Thus, in populations such as this one with relatively good ART penetrance but limited screening and treatment for hypertension, diabetes, and hyperlipidemia, conventional risk factors may be more important than in populations with either low ART penetrance or high ART penetrance and aggressive screening and treatment of conventional vascular risk factors, in which HIV-related factors may be a more significant contributor to stroke risk.

Our finding that PLWH and stroke had been diagnosed more recently than PLWH controls without stroke is concordant with a prior case-control study conducted in Malawi, which compared 69 HIV-positive stroke cases to 96 HIV-positive stroke-free controls [30]. This study found that the risk of stroke was higher in the first 6 months after starting ART. Additionally, a large prospective study, the Data Collection on Adverse Events of Anti-HIV Drugs study reported a high rate of vascular events in the first year of treatment [25]. A case-control study from Portugal, comparing 17 HIV-positive stroke cases to 23 controls did not find a significant difference in the median number of months living with HIV infection (107 versus 137 months, $p = .111$), although there was a high rate of injection drug use in this population, which could be contributing to stroke risk unrelated to HIV history [17]. It is uncertain why the risk of stroke would be highest earlier in the course of disease. Some authors have proposed that stroke in PLWH may sometimes be a manifestation of immune reconstitution inflammatory syndrome (IRIS) [30], although more research is needed both to confirm this association and to understand the pathophysiology. Despite concerns that ART might contribute to stroke risk [31–42], in our population 37% of HIV-positive stroke cases were not on ART and the median time from HIV diagnosis to stroke was only 1 year. So although small numbers of patients limited our ability to investigate the relative risks of different regimens, long-term metabolic consequences of ART were not likely a significant contributor in many patients.

4.3. Limitations, bias, and generalizability

Limitations of the study include a relatively small sample size, reliance on CT imaging rather than MRI, and lack of long-term follow up. Sample size was lower than expected, as during the period of the study most patients with stroke were cared for at local hospitals rather than being referred to a tertiary facility. This reduced statistical power. Less than half of all patients admitted with potential strokes were enrolled in the study. Inability to consent and/or death prior to consent may have limited our ability to enroll the most severely ill patients. Conversely, discharge prior to enrollment may have limited our ability to enroll patients with mild strokes. This introduces the possibility of selection bias, which could have systematically excluded the most severely ill subjects and/or subjects with late stage HIV. Limited diagnostic testing is another significant limitation. The absence of vascular imaging such as carotid ultrasound and magnetic resonance arteriography (MRA) in most patients likely led to an underestimation of the contribution of large vessel atherosclerosis to stroke in this study. Although outpatient records were reviewed whenever possible to evaluate past medical history, the study is also limited by dependence on subjects or family members to report risk factors. Risk factors such as hypertension, diabetes, and hyperlipidemia are underdiagnosed in Botswana, likely leading to an underestimation of the contribution of these risk factors to stroke. Our study was not designed to detect evidence of IRIS. Control subjects did not undergo neuroimaging and we were not able to assess for silent cerebrovascular disease in these subjects. Finally, this study was conducted at a single referral center, and thus patients in the study may not be representative of patients in other areas. Nevertheless, we expect that these results should apply to other populations living with HIV in Sub-Saharan Africa.

5. Conclusion and future directions

Patients living with HIV are at increased risk of stroke at younger ages, and have high rates of lacunar strokes, suggesting that small vessel disease is a significant contributing factor. Further studies are necessary to better characterize this pathophysiology. Our study identified several risk factors for stroke that should be evaluated in patients with HIV, including hypertension, alcohol use, and smoking, all of which could be screened for and targeted in routine outpatient visits. Further studies are necessary to identify optimal prevention and treatment strategies for patients with HIV at risk of stroke.

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