RESEARCH ARTICLE

HIV Infection and 90-Day Stroke Outcomes in Uganda

A Prospective Observational Cohort Study

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Abstract

Background and Objectives

Little is known about the impact of HIV infection on the clinical presentation and outcomes after stroke in the modern antiretroviral therapy (ART) era. We aimed to compare stroke characteristics and outcomes between persons with HIV (PWH) and without HIV (PWOH) presenting with stroke in Uganda.

Methods

We conducted a matched cohort study at Mulago National Referral Hospital and Mbarara Regional Referral Hospital between January 2018 and November 2020. We enrolled consecutive PWH presenting with CT-confirmed acute or subacute stroke (symptom onset ≤14 days) and matched them by sex and stroke type to 2 consecutive available PWOH admitted to the same hospital. We obtained baseline clinical data and followed participants for 90 days from the day of clinical presentation. We compared stroke severity (defined by the NIH stroke scale [NIHSS]) and 90-day all-cause mortality and morbidity (using the modified Rankin Scale [mRS]) by HIV serostatus with and without adjustment for confounders.

Results

We enrolled 105 PWH and 157 PWOH with stroke. PWH were younger (mean [SD] age 49 [14] vs 59 [16] years, $p < 0.001$), and nearly 80% (82/105) were on ART for a median of 5 years and a median CD4 count of 214 cells/uL (interquartile range 140, 337). Compared with PWOH, PWH presented with a 3-point lower median NIHSS (16 vs 19, $p = 0.011$), a 20% lower proportion of all-cause mortality at 90 days ($p = 0.001$), and had less disability at 90 days (median mRS 4 vs 5, $p = 0.004$). Age and NIHSS-adjusted odds ratio of 90-day all-cause mortality in PWH compared with PWOH was 0.45 (95% CI 0.22–0.96, $p = 0.037$).

Discussion

In the modern ART era, PWH with acute stroke in Uganda present with modest stroke and are significantly less likely to die within 90 days than PWOH. This potentially reflects the protective effects of ART, enhanced health care access, and their younger age at stroke presentation.

Introduction

HIV infection increases the risk of stroke by 40%–100% in both resource-rich and resource-limited settings.[1,2] Data from the pre-antiretroviral therapy (ART) era suggest that the

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increased risk of stroke among people with HIV (PWH) was primarily driven by immunosuppression, opportunistic infections, and HIV-associated vasculopathy.[3-5] However, studies in the era of widespread ART availability demonstrate a decreasing role of opportunistic infections in stroke pathogenesis, and instead, stroke in this population may be driven by other noninfectious, traditional stroke risk factors such increasing age, hypertension, dyslipidemia, and type 2 diabetes.[6,7] Furthermore, emerging literature suggests that the risk of stroke and other cardiovascular diseases is reducing in PWH initiating early ART.[8,9] Whether these reductions in stroke risk and rates of opportunistic infections is associated with an improvement in post-stroke outcomes in the ART era in Sub-Saharan Africa (SSA) is not well elucidated.

In the pre-ART era, PWH in SSA had poor stroke outcomes.[5] However, there are few data in the modern ART era about whether the beneficial effects of ART[10] extend to improved outcomes after stroke. PWH present with stroke at a younger age,[5,7] which may infer improved prognosis but result in greater reductions in disability-free years of life. Similarly, broad uptake of ART may also have countervailing effects—potentially increasing the risk of stroke risk factors.[11,12] We sought to respond to this knowledge gap by enrolling a prospective longitudinal matched cohort of PWH and people without HIV (PWOH) presenting with stroke in Uganda to better understand contributions of HIV to stroke outcomes and identify potential interventions that might enable reductions in stroke-related morbidity and mortality in PWH.

Methods

Study Setting and Available Stroke Care at the Hospital Sites

We enrolled PWH and PWOH presenting with stroke to Mbarara Regional Referral Hospital (MRRH) and Mulago National Referral Hospital (MNRH), the 2 largest hospitals in Uganda. Patients with stroke typically present to the emergency room of both hospitals using privately arranged transportation. Both hospitals have onsite CT scan, but there was no available magnetic resonance imaging scanner at the time of conduct of this study. On arrival, patients with stroke are clinically stabilized in the emergency ward, later transferred, and followed up in the general medical ward at MRRH or neurology ward at MNRH. At either hospital, no dedicated stroke unit existed during the conduct. Acute stroke care is primarily focused on conservative medical management to prevent or delay stroke complications. Inpatient physical therapy is available but limited. Postdischarge, most patients are typically followed in the community at the lower-level health facilities and district hospitals, with minimal formal poststroke rehabilitation services. In addition, PWH are followed in HIV clinics after discharge.

Study design and Recruitment Process: We conducted a matched cohort study including PWH (cases) and PWOH (controls) presenting with stroke to MRRH and MNRH. To enroll a balanced cohort for sex and stroke type, we first recruited consecutive PWH presenting to the study hospitals with CT-confirmed stroke within 14 days of symptom onset. For each PWH enrolled, we enrolled the next 2 PWOH who were matched by sex and stroke type (ischemic vs hemorrhagic). Therefore, PWH were enrolled consecutively while PWOH were only enrolled after the PWH case had been enrolled.

Data Collection

Participants were enrolled after initial stroke management had been administered by the clinical team. Participant and/or their family member reported sociodemographic characteristics and clinical (symptoms, medication, and medical history) data. Intersex identities were not evaluated. For PWH, CD4 count and ART history were also collected. Study questionnaires were adapted from the INTERSTROKE study.[13] We collected blood and measured random blood glucose, lipids, HIV tests for participants not taking ART, CD4 cell count if not recently (<3 months) tested, complete blood count, and serum electrolytes. A study physician examined participants for stroke signs and measured stroke severity with the NIH Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS). Brain CT scans were interpreted by the hospital radiologists and then reviewed for research purposes by study physicians (A.A.M., A.K., A.M.) before enrollment. CT scan results with equivocal findings for stroke were overread by the study radiologist (A.M.) and vascular neurologist (C.O.C.). Finally, participants were followed until discharge to collect in-hospital treatments received and outcome (e.g., death, discharge, transfer) data. For those discharged before day 90, a final study visit was conducted at 90 days to determine vital status and modified Rankin Scale score (mRS). The evaluation of mRS score was performed by a single trained assessor at each site.

Sample Size and Statistical Analysis

We powered the study to detect a crude difference in poor stroke outcomes between PWH and PWOH. Poor stroke outcomes were defined as having an mRS of 2–6 at 90 days, where 2 represents slight disability after stroke and 6 is death. We chose the 90-day period because it is the traditional timeline used to evaluate poststroke outcomes in clinical trials.[14,15] Based on previous data from SSA on estimates of stroke outcomes in PWH and the PWOH[16,17] and an estimated attrition rate of 10%, we calculated a sample size of 100 PWH and 200 PWOH to have sufficient power to detect a crude difference of 10%–20% in 90-day mRS (the primary outcome) between the 2 groups. The study was halted before completion of goal enrollment (262/300 enrolled; 87% completion) because of financial limitations caused by prolonged enrollment interruptions during the COVID-19 pandemic.

We compared clinical and demographic characteristics between PWH and PWOH. We then compared stroke severity at enrollment and stroke outcomes, including stroke outcomes (90-day mRS 2–6 vs 0–1: primary outcome) and 90-day all-cause mortality (secondary outcome). Chi-square analyses were used to compare categorical variables. T-tests were used to compare continuous parametric variables while Wilcoxon rank-sum tests were used to compare nonparametric continuous variables.

Finally, we fit logistic regression models with all-cause mortality at 90 days after presentation as the outcome and HIV status as the exposure, adjusted for confounding variables, including age, sex, fever, dyspnea, diabetes, seizure, and stroke severity (NIHSS score). Two groups of regression models were fit: models with and without stroke severity at presentation, as defined by NIHSS, to estimate the association of HIV serostatus with stroke outcome before and after accounting for HIV-associated differences in stroke severity at presentation. To select variables for the multivariable model, we first added sociodemographic and clinical variables that have been previously shown to be associated with stroke outcomes such as age, sex, stroke type, and stroke severity.[17-19] We then excluded collinear variables (e.g., temperature, fever, and white blood cell count; dyspnea and dysphagia; level of consciousness, NIHSS, GCS, and stroke type) and replaced all individual stroke signs and symptoms with the NIHSS. As an example, stroke type (hemorrhagic vs ischemic) was not added to models because it was not significant on univariable analysis, and it correlated with stroke severity and level of consciousness. After fitting our final model, we assessed for collinearity by confirming the variation inflation factor was less than 2 for all included variables.[20]

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approvals were obtained from Partners Institutional Review Board (Boston), Mbarara University Research Ethics Committee (Mbarara, Uganda), Mulago Research Ethics Committee (Kampala, Uganda), and the Uganda National Council of Science and Technology (Kampala, Uganda). All participants with capacity provided written informed consent. Written consent was provided by a surrogate for participants who did not have medical capacity to provide consent such as those with aphasia and those with reduced level of consciousness.

Data Availability

Anonymized data not published within this article will be made available at request from any qualified investigator.

Results

Participant Characteristics

From January 2018 through November 2020, we screened 370 patients presenting with stroke (Figure 1). After excluding 108 patients, we enrolled 262 participants (105 PWH and 157 PWOH). Three PWOH were lost to follow-up, leaving 259 participants with data available for 90-day analyses. Of those analyzed, 206 (79 PWH [38%] and 127 PWOH [62%]) participants were enrolled from Mulago National Referral Hospital (MNRH) and 56 (27 PWH [48%] and 29 PWOH [52%]) from MRRH.

Participant characteristics are summarized in Table 1. The mean age for the total cohort was 55 years (standard deviation [SD] 16), and 52% (135/262) were men. The majority (184/262, 70%) had ischemic stroke. Characteristics were similar by HIV serostatus, except PWH were younger (mean age 49 years [SD 14] vs 59 years [SD 16]), were more likely to be men (63/105, 60% vs 72/157, 46%), more likely to present with ischemic stroke (81/105, 77% vs 103/157, 66%), and more likely to have had any formal education (Table 1). There was no difference in time from stroke onset to hospital presentation (Table 1). The median CD4 count was 214 (interquartile range [IQR] 140–337) cells/uL. Most of the PWH (82/105, 78%) were on ART for a median of 5 years (IQR 1–10 years).

Stroke Severity at Enrollment

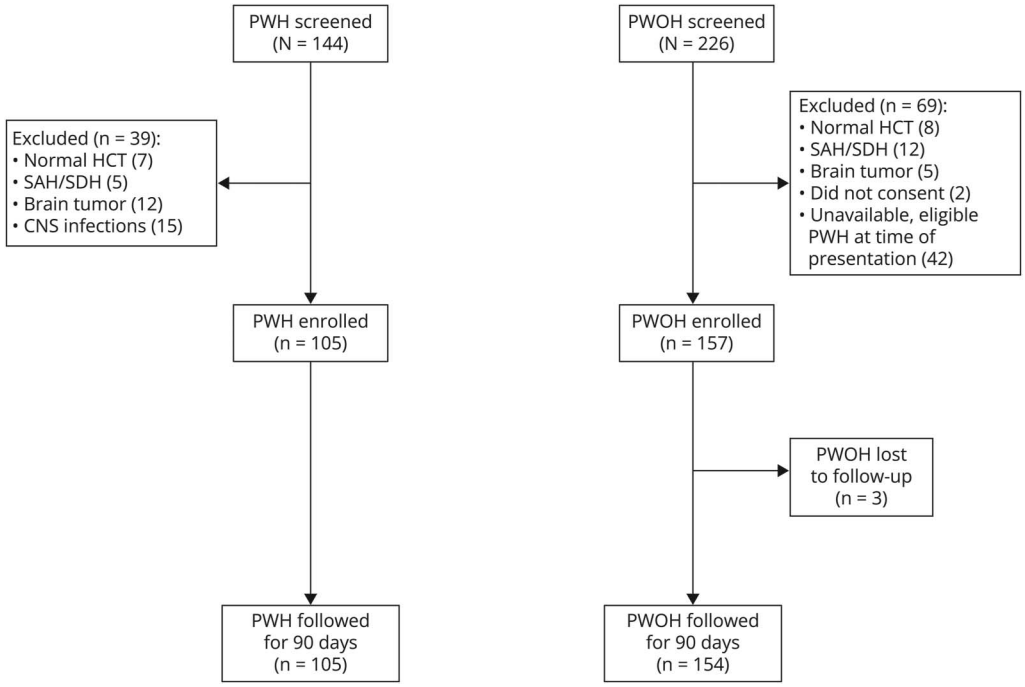
Stroke severity scores at presentation were higher in PWOH as compared with PWH ($p = 0.013$) (Figure 2A). In the total cohort, 65% of (100/154) PWOH vs 50% (53/105) PWH had severe NIHSS (>15), 29% (44/154) PWOH vs 35% (37/105) PWH had moderate stroke (NIHSS 9–15), and 6% (10/154) PWOH vs 15% (15/105) PWH had mild stroke (Figure 2A). The median (IQR) NIHSS score was 19 (IQR, 12–24) in PWOH vs 16 (IQR, 11–22) in PWH, $p = 0.013$ (Table 1). This difference in stroke severity scores was significant in those with ischemic stroke ($p = 0.011$) but not in those with hemorrhagic stroke ($p = 0.50$) (Figure 2A). There was a higher proportion of severe stroke (NIHSS >15) in PWOH with hemorrhagic stroke as compared with PWH with hemorrhagic stroke (61% vs 46% $p < 0.001$) (Figure 2A). PWOH also tended to have lower Glasgow Coma Scale (GCS) scores though not statistically significant at 5% alpha (11 [IQR 10–14] in PWOH vs 12 [IQR 10–15] in PWH, $p = 0.056$).

PWOH were also more likely to present with stroke-related complications such as abnormal chest auscultatory signs and a higher white blood cell count, suggesting the presence of aspiration pneumonia at the time of presentation (Table 1). For instance, 15% of PWOH had abnormal auscultatory chest findings as compared with 7% in PWH, $p = 0.035$.

Inpatient Management

None of the participants with ischemic stroke received intravenous thrombolytic therapy because of unavailability. Noteworthy, 8% (8/105) of PWH and 1% (1/154) of PWOH presented within the recommended 4.5-hour thrombolytic window. In those with ischemic stroke, an

Figure 1 Flowchart Showing the Number of Participants Screened and Enrolled



antiplatelet agent such as clopidogrel or aspirin was more likely to be administered to PWOH than PWH (98/101, 97% vs 72/81, 88% in PWH, $p = 0.002$), and only one participant (1/182, 1%) received anticoagulant therapy. Rates of initiation of any antihypertensive medication by the second day of admission was similar in both groups (101/154, 66% in PWOH vs 57/105, 54% in PWH, $p = 0.063$).

Stroke Outcomes

Poor stroke outcomes, defined by an mRS between 2 and 6, were nearly ubiquitous at 90 days in this cohort, so no crude difference in this outcome was found (152/154, 99% in PWOH vs 101/105, 96% in PWH, $p = 0.187$, Table 2). However, PWOH had higher 90-day crude all-cause mortality (mRS = 6) than PWH (74/154, 48% in PWOH vs 29/105, 28% in PWH, $p = 0.001$) (Figure 2B) and a higher unadjusted median 90-day mRS (5 [IQR 4–6] in PWOH vs 4 [IQR 3–4] in PWH, $p = 0.004$) (Table 2). Similarly, there were approximately twice as many in-hospital deaths in PWOH than PWH, but this difference did not reach statistical significance (40/154, 26% in PWOH vs 13/105, 12% in PWH, $p = 0.146$) (Table 2). Furthermore, a higher all-cause mortality rate in PWOH was observed when 90-day all-cause mortality outcomes were analyzed according to hospital site. There were more deaths in PWOH as compared with PWH participants enrolled at MRRH (MRRH PWOH 14/29 [48%] vs MRRH PWH 6/27 [22%] and at MNRH (MNRH PWOH 60/128 [47%] vs MNRH PWH 23/80 [29%]).

In multivariable regression models adjusting for age, sex, presence of fever, stroke type, presence of dyspnea, presence of diabetes, and the presence of seizure, PWH had significantly lower odds of all-cause mortality than PWOH (adjusted odds ratio [AOR] 0.39, 95% CI 0.20–0.77, $p = 0.007$) (Table 3). The adjusted odds of all-cause mortality was lower in PWH even after adjusting for stroke severity (AOR 0.45, 95% CI 0.22–0.96, $p = 0.037$). Other significant associations of 90-day all-cause mortality included age (AOR 1.02, 95% CI 1.00–1.05, $p = 0.038$) and NIHSS score (AOR 1.22, 95% CI 1.15–1.31, $p < 0.001$).

Discussion

We found that PWH presenting with stroke in Uganda during the ART era had significantly less disability and lower odds of 90-day all-cause mortality than their counterparts without HIV. The differences in stroke outcomes observed remained consistent after adjustment for age, sex, stroke severity, and other potential confounders. These data show that, with widespread use of ART, the severity and disability associated with stroke may be mitigated among PWH in Sub-Saharan Africa.

Our results contrast with historical data on poststroke outcomes in the pre-ART and early ART eras, which suggested that HIV infection was inversely associated with stroke outcomes. For example, a landmark study from Malawi including PWH, most of whom were not on ART, showed higher rates

Table 1 Sociodemographic, Clinical, and Radiologic Baseline Data

	Total n = 262	PWOH n = 157	PWH n = 105	*p* Value
Age, mean (SD)	55 (16)	59 (16)	49 (14)	<0.002
Men, n (%)	135 (52)	72 (46)	63 (60)	0.025
Employment, n (%)				
Peasant farmer	76 (29)	47 (30)	29 (28)	0.325
Business owner	104 (40)	60 (38)	44 (42)	
Professional	31 (12)	16 (10)	15 (14)	
Unemployed or retired	51 (19)	34 (22)	17 (16)	
No formal education, n (%)	57 (22)	43 (27)	14 (13)	0.030
Hypertension, n (%)	144 (55)	94 (60)	50 (48)	0.051
Current or former smoker, n (%)	40 (15)	20 (13)	20 (19)	0.306
Diabetes mellitus, n (%)	45 (17)	27 (17)	18 (17)	0.991
Atrial fibrillation on EKG, n (%)	9 (3)	8 (5)	1 (1)	0.216
Heart failure history, n (%)	9 (3)	6 (4)	3 (3)	0.668
Stroke duration, d, median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)	0.105
Aphasia, n (%)	192 (73)	120 (76)	72 (69)	0.159
Dysphagia, n (%)	60 (23)	39 (25)	21 (20)	0.361
Dyspnea, n (%)	46 (18)	27 (17)	19 (18)	0.027
Clinical seizure, n (%)	42 (16)	24 (15)	18 (17)	0.705
Fever history, n (%)	43 (16)	20 (13)	23 (22)	0.052
Systolic blood pressure at admission, median (range), mm Hg	151 (128–170)	153 (131–173)	144 (123–168)	0.075
Diastolic blood pressure at admission, mean (SD), mm Hg	91 (78–103)	92 (80–103)	90 (75–102)	0.342
Temperature, median (IQR), °C	37 (36–37)	37 (36–37)	37 (36–37)	0.337
NIHSS Score, median (IQR)	17 (11–23)	19 (12–24)	16 (11–22)	0.013
Glasgow Coma Scale score, median (IQR)	11 (10–14)	11 (10–14)	12 (10–15)	0.056
Abnormal chest auscultatory findings, n (%)	31 (12)	24 (15)	7 (7)	0.035
Prestroke mRS 0–1, n (%)	225 (86)	136 (87)	89 (85)	0.579
Serum white blood cell count, $\times 10^9$ cells per liter, median (IQR)	8 (7–11)	9 (7–11)	7 (5–9)	<0.001
Serum Sodium, mmol/L, median (IQR)	139 (136–143)	139 (135–143)	139 (136–143)	0.942
Serum LDL, mmol/L, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	0.543
Stroke types, n (%)				
Ischemic stroke	184 (70)	103 (66)	81 (77)	0.045
Hemorrhagic stroke	78 (30)	54 (34)	24 (23)	
Ischemic stroke locations, n (%)				
Anterior circulation	155 (84)	90 (87)	65 (80)	0.188
Posterior circulation	29 (16)	13 (13)	16 (21)	

Continued

Table 1 Sociodemographic, Clinical, and Radiologic Baseline Data *(continued)*

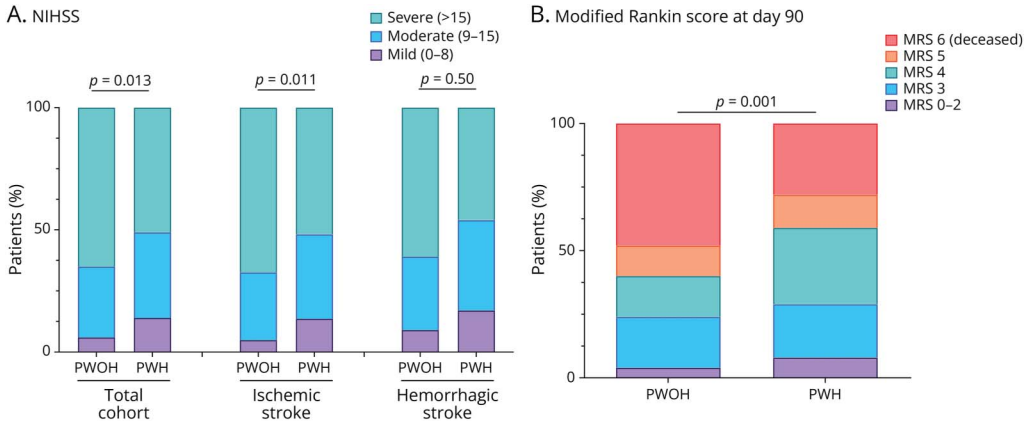
	Total n = 262	PWOH n = 157	PWH n = 105	*p* Value
Hemorrhagic stroke locations, n (%)				
Thalamus and basal ganglia	62 (79)	43 (80)	19 (79)	0.968
Brainstem and cerebellum	5 (6)	3 (6)	2 (8)	
Lobar regions	11 (14)	8 (15)	3 (13)	

Abbreviations: IQR = interquartile range; mRS = modified Rankin Scale score; NIHSS = NIH Stroke Scale; PWH = persons with HIV infection; PWOH = persons without HIV infection.

of poor stroke outcomes in PWH at 6 weeks, although this was less evident after 6 months.[16] Another study from the pre-ART era in Benin, including 114 PWH with median CD4 count of 119 cells/mm^3, found that PWH had higher stroke severity, higher rates of sepsis, and higher rates of 30-day all-cause mortality as compared with those without HIV infection.[21] Finally, a study using national data of hospitalized patients in Thailand found that HIV infection was associated with higher odds of inpatient all-cause mortality and sepsis.[22] Notably, PWH in those studies were largely presenting with advanced disease, with immunosuppression and opportunistic infections hypothesized to be major contributors to both stroke etiology and poor poststroke outcomes.

More recent studies from Zambia,[23] South Africa,[24] Cameroon,[25] and Botswana have suggested that short-term outcomes have improved in the ART era, with data generally demonstrating that the rates of in-hospital all-cause mortality are similar between PWH and PWOH. Our study is in keeping with these studies, suggesting that poststroke outcomes are improving among PWH relative to PWOH in Uganda. While the mechanisms for these improved outcomes are not fully understood, multiple potential factors could be responsible. The widespread use of ART in PWH is expected to lead to improved stroke outcomes both through direct reductions in opportunistic infection risk[26,27] as well as secondary benefits on health and hospital-associated complications.[28] HIV associated opportunistic infections are known to contribute to higher all-cause mortality and in-hospital complications which could in turn lead to poor stroke outcomes. In addition, PWH tend to present with stroke at younger ages,[2,5] and thus, survivors may have better neuroplasticity and poststroke recovery long-term.[29] In relation to stroke mechanisms, several studies have indicated that PWH have a propensity toward developing small vessel disease–related ischemic stroke,[30,31] which is reflected by a lower NIHSS score in our group of patients. This mechanism is linked to better stroke outcomes.[32] Finally, emerging data from SSA show that PWH have improved cardiometabolic health indicators and outcomes,[33,34] possibly because of the additional primary care services provided by HIV care programs in the region. These programs essentially mandate that PWH routinely engage with the health care system for HIV treatment and may derive secondary benefits such as routine blood pressure checks, weight monitoring, and smoking cessation support. Consequently, PWH have been found to have better control of cardiometabolic risk factors such as hypertension, hyperlipidemia, and diabetes.[34-36]

Figure 2 Stroke Severity at Presentation (NIHSS) and Disability at 90 days (mRS)



(A) Bar graphs showing a comparison of stroke severity scores categorized into mild stroke (NIHSS 0–8), moderate stroke (NIHSS 9–15), and severe stroke (NIHSS >15). (B) Bar graphs show a comparison of mRS at 90 days by HIV serostatus. mRS = modified Rankin Scale Scores; NIHSS = NIH stroke scale.

Table 2 Study Outcomes; Mortality and Morbidity Scores at 90 Days

Outcomes	Total n = 259	PWOH n = 154	PWH n = 105	*p* Value
mRS category scores, n (%)				
mRS 0–1	6 (2)	2 (1)	4 (4)	0.187
mRS 2–6	253 (98)	152 (99)	101 (96)	
Mortality at 90 d (mRS = 6), n (%)	103 (40)	74 (48)	29 (28)	0.001
In-hospital mortality (mRS = 6), n (%)	53 (20)	40 (26)	13 (12)	0.146
Median mRS score at 90 d in the total cohort, median (IQR)	5 (3–6)	5 (4–6)	4 (3–6)	0.004

Abbreviations: IQR = interquartile range; mRS = modified Rankin Scale score; PWH = persons with HIV infection; PWOH = persons without HIV infection.

Future work should explore if and to what magnitude such relationships help mediate improved outcomes after stroke in this population.

We postulate that PWH who are engaged in routine ART care are more likely to receive posthospital stroke follow-up and care than PWOH which may mean less risk of secondary stroke complications. Our study likely suggests that long-term engagement in HIV care and ART usage is associated with improved HIV-related outcomes[37] and better cardiovascular outcomes, possibly leading to improved stroke outcomes. It is therefore worth noting that PWH who do not continuously engage in routine HIV care either because of socioeconomic reasons or because of being part of a disadvantaged group are unlikely to have the improved stroke outcomes noted in this study. PWH who belong to sexual and gender minority groups or internally displaced persons/refugees are more likely to experience health care disparities across the continuum of care because of poor health care access, thus leading to multiple primary and secondary cardiovascular complications[38] in addition to worse outcomes of HIV infection itself. Therefore, it is important to leverage the HIV care system to provide comprehensive primary health care in all PWH but especially at-risk groups such as those belonging to sexual and gender minority groups, internally displaced persons, and refugees because they are less likely to access the health care system outside of the HIV clinic. Thus, clinicians and health care leaders in the region, and globally, ought to ensure that individuals belonging to such disadvantaged populations are actively sought and specifically targeted with tailored interventions aimed at fostering continued and active participation in routine HIV care.

Notwithstanding the relatively improved outcomes after stroke among PWH, all-cause mortality and disability were extremely high in both groups. The median 90-day mRS score in entire cohort was 5 (representing severe disability requiring constant nursing and care giver support), and approximately 40% of individuals were deceased by 90 days. These results are consistent with other studies on stroke outcomes in SSA.[17,18] Several factors are likely to cause such poor stroke outcomes in the region. First, individuals present with severe disease in our cohort (overall median NIHSS of 18), significantly higher than reported NIHSS scores at presentation in resource-rich settings (e.g., 5 in Japan[39] and 3 in the United States).[40] Similarly, time to hospital presentation was relatively late at a median of 3 days after symptom onset, compared with the United States where the mean time to presentation is approximately 15 hours, and nearly 50% of individuals present within 4 hours.[41] Therefore, individuals with stroke presenting to hospitals at tertiary centers in Uganda present late, often with complications such as aspiration pneumonia which inevitably contribute to poor stroke outcomes. Finally, international standard stroke management resources, such as intravenous thrombolysis[14] and neurologic intensive care units, are sparse if not totally absent in much of the region[42] which means that even those who present early are unlikely to get optimal care. These data reinforce the critical need to improve stroke outcomes in SSA through multifaceted approaches including strengthening community awareness to promote early hospital presentation,[43,44] improving acute stroke treatment capabilities at referral hospitals, and most importantly, promoting primary stroke prevention measures.[43]

Our study was strengthened by a relatively large sample size of PWH and prospective observation. This is the largest prospective study of stroke outcomes among PWH in SSA in the ART era, which enables precise estimation of outcomes. The study also had limitations. Matching was incomplete, which we accounted for by adjusting for confounders, such as stroke severity, sex, and age. The study was underpowered to detect smaller differences in stroke outcomes by subgroups, such as those with hemorrhagic vs ischemic stroke. We were unable to compare stroke outcomes using our a priori definition of mRS 0–1 vs mRS 2–6 because of an extremely small number of people with an mRS of 0–1 at the study conclusion. Referral bias is likely to have influenced the generalizability of this study. We recruited participants from 2 tertiary hospitals in Uganda, where more complex cases are likely to be referred. However, our study provides a representation of tertiary referral hospitals in SSA, which is precisely where

Table 3 Predictors of 90-Day Mortality on Regression Analysis

	Univariable analysis		Multivariable analysis model 1 without NIHSS		Multivariable analysis model 2 with NIHSS	
Variable	OR (95% CI)	*p* Value	AOR (95% CI)	*p* Value	AOR (95% CI)	*p* Value
Age (per year)	1.03 (1.02–1.05)	<0.001	1.04 (1.02–1.06)	0.001	1.02 (1.00–1.05)	0.038
Sex						
Women	REF					
Men	0.83 (0.50–1.37)	0.463	1.10 (0.60–1.98)	0.773	1.44 (0.72–2.90)	0.300
HIV status						
PWOH	REF					
PWH	0.41 (0.24–0.70)	0.001	0.37 (0.20–0.72)	0.004	0.45 (0.22–0.96)	0.037
NIHSS (per unit increase)	1.26 (1.19–1.34)	<0.001			1.22 (1.15–1.31)	<0.001
Stroke type						
Ischemic stroke	REF					
Hemorrhagic stroke	1.30 (0.75–2.22)	0.349				
Fever at admission						
Absent	REF					
Present	2.60 (1.32–5.11)	0.006	3.22 (1.38–7.52)	0.007	1.45 (0.55–3.83)	0.455
Dyspnea at admission						
Absent	REF					
Present	5.91 (2.88–12.12)	<0.001	6.50 (2.84–14.90)	<0.001	2.26 (0.88–5.82)	0.090
Aphasia at admission						
Absent	REF					
Present	6.53 (3.07–13.90)	<0.001				
Dysphagia at admission						
Absent	REF					
Present	3.98 (2.15–7.37)	<0.001				
Diabetes at admission						
Absent	REF					
Present	2.07 (1.07–3.98)	0.030	1.95 (0.92–4.14)	0.080	1.73 (0.71–4.24)	0.229
Seizure at admission						
Absent	REF					
Present	2.96 (1.49–5.84)	0.002	2.85 (1.27–6.42)	0.011	2.32 (0.92–5.88)	0.077
Temperature (per unit increase)	1.66 (1.21–2.27)	0.002				
White blood cell count (per unit increase)	1.17 (1.08–1.27)	<0.001				
Hypertension history at admission						
History of prior stroke						
Absent	REF					
Present	1.01 (0.43–2.34)	0.980				
Absent	REF					
Present	1.18 (0.71–1.95)	0.519				
Stroke duration (per unit increase in d)	0.95 (0.89–1.02)	0.190				
Admission Glasgow Coma Scale score, per unit increase	0.59 (0.52–0.68)	<0.001				

TAKE-HOME POINTS

- In the antiretroviral therapy era, people with HIV presenting with stroke in Uganda now tend to be on antiretroviral therapy for many years, although persistently low CD4 counts are common in this population.
- People without HIV present with more severe strokes than people with HIV in Uganda, as evidenced by a higher median NIH Stroke Scale score.
- Stroke outcomes are poor overall with a mortality rate at 90 days of 40% in the entire cohort.
- Compared with people with HIV infection, those without HIV infection have higher all-cause mortality and greater disability 90 days after stroke.

most strokes are treated, irrespective of HIV serostatus. We were also unable to assess for all vascular risk factors of interest such as carotid artery stenosis, cardioembolic sources, and virologic suppression, which can affect stroke recurrence rates and outcome.[45,46] We did not collect specific data on the frequency of outpatient visits with a medical provider in the peristroke period, which is an important factor that can potentially influence stroke outcomes. Finally, reliance on CT scan imaging for stroke diagnosis can either lead to exclusion of those with false-negative CT scan results (poor sensitivity) or enrollment of those with stroke mimics such as brain tumor or brain infections (poor specificity). However, this limitation is less of a concern in those presenting after the first 6 hours of stroke onset because of the presence of already established areas of well-defined hypodensity in the appropriate vascular territory. The specificity of CT scan for stroke detection is estimated at 92% for those presenting within 6 hrs and 100% in those presenting after 12 hrs.[47] Participants in our study presented on average after 3 days from stroke onset, with severe stroke syndromes, thus potentially making stroke misclassification less of a concern.

In summary, all-cause mortality at 90 days after stroke presentation and stroke morbidity outcomes were improved among PWH compared with PWOH in Uganda in the current ART era. Nonetheless, stroke outcomes were generally poor, with nearly 40% all-cause mortality in the overall cohort within 3 months. Our data reinforce the benefits of ART on cardiovascular outcomes among PWH but also the important and urgent need to improve resource allocation to stroke prevention and care in the region.

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Acan Moses, MBChB, MMED	Department of Radiology, Mbarara University of Science and Technology, Uganda	Major role in the acquisition of data; analysis or interpretation of data; additional contributions (in addition to one or more of the above criteria)
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Continued

Appendix *(continued)*

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