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An analysis of stroke risk factors by HIV serostatus in Uganda: Implications for stroke prevention in sub-Saharan Africa

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Abstract

Objective: HIV infection is an important stroke risk factor in sub-Saharan Africa. However, data on stroke risk factors in the era of antiretroviral therapy (ART) are sparse. We aimed to determine if stroke risk factors differed by HIV serostatus in Uganda.

Methods: We conducted a matched cohort study, enrolling persons living with HIV (PWH) with acute stroke, matched by sex and stroke type to HIV uninfected (HIV-) individuals. We collected data on stroke risk factors and fitted logistic regression models for analysis.

Results: We enrolled 262 participants:105 PWH and 157 HIV-. The median ART duration was 5 years, and the median CD4 cell count was 214 cells/uL. PWH with ischemic stroke had higher odds of hypertriglyceridemia (AOR 1.63; 95% CI 1.04, 2.55, p=0.03), alcohol consumption (AOR

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Declaration of Competing Interest

None

2.84; 95% CI 1.32, 6.14, p=0.008), and depression (AOR 5.64; 95%CI 1.32, 24.02, p=0.02) while HIV- persons with ischemic stroke were more likely to be > 55 years of age (AOR 0.43; 95%CI 0.20–0.95, p=0.037), have an irregular heart rhythm (AOR 0.31; 95%CI 0.10–0.98, p=0.047) and report low fruit consumption (AOR 0.39; 95%CI 0.18–0.83, p=0.014). Among all participants with hemorrhagic stroke (n=78) we found no differences in the prevalence of risk factors between PWH and HIV-.

Conclusions: PWH with ischemic stroke in Uganda present at a younger age, and with a combination of traditional and psychosocial risk factors. By contrast, HIV- persons more commonly present with arrhythmia. A differential approach to stroke prevention might be needed in these populations.

Keywords

HIV infection; Stroke; risk factors; psychosocial factors; hypertension; sub Saharan Africa; Uganda

Introduction

The incidence of stroke is rising in sub-Saharan Africa (SSA), and HIV infection is thought to substantially contribute to this rise, with an estimated population attributable fraction (PAF) for stroke of 15%.[1] The increasing availability of highly active antiretroviral therapy (ART) for persons living with HIV (PWH) in SSA, suggests that PWH might now have similar stroke risk factor profiles as HIV-uninfected (HIV-) individuals[2] due to protective effects of ART in reducing HIV related infectious complications associated with stroke. However, data on stroke risk factors in the ART era in SSA remain sparse. We, therefore, aimed to determine if stroke risk factors differed by HIV serostatus in cohorts of PWH on ART and HIV- adults admitted to hospitals in two centers in Uganda.

Methods

We conducted a matched cohort study of PWH (cases) and HIV- comparators (controls) who were matched for sex and stroke type. Cases and controls were adults presenting to Mbarara Regional Hospital (Mbarara, Uganda) and Mulago National Hospital (MNH; Kampala, Uganda) with radiographically confirmed acute stroke, excluding those with subarachnoid hemorrhage and subdural hemorrhage. Study personnel first identified PWH presenting with clinical signs of focal cerebral dysfunction lasting 0–14 days and referred them for a study funded brain non contrasted computerized tomography (CT) scan, if not yet completed. A radiologist interpreted all CT scans, with the radiologic findings confirmed by a study physician (A.A.M, A.M, A.K, S.O, K.A). Only PWH with CT findings consistent with acute stroke were enrolled. On average, we enrolled about 2 PWH with stroke at Mulago National Hospital per month and 1 PWH with stroke at Mbarara Regional Hospital, per month. Following enrollment of PWH, we subsequently enrolled the next two available HIV- individuals (2:1 matching) presenting to the same center with stroke, matched to PWH by sex and stroke type (ischemic vs. hemorrhagic). This matching criteria therefore meant that the enrollment of PWH was consecutive but that of HIV- individuals was not.

We collected data on sociodemographic characteristics, presenting symptoms, HIV and ART history and current medications using a standardized questionnaire adapted from the 2016 INTERSTROKE study.[1] A study physician obtained data on clinical signs, including the National Institutes of Health Stroke Scale (NIHSS) score. We collected blood samples for random blood glucose, lipid profiling, HIV testing and complete blood count.

We defined hypertension as having a self-reported history of hypertension or a measured blood pressure ≥ 140/90 mmHg, derived from an average of three measurements taken on admission and the morning day after admission. Definitions of all other risk factors are presented in Supplementary Table 1.

Sample size estimation and statistical analysis

This study represents an analysis of baseline data from an ongoing study evaluating the impact of HIV infection on stroke outcomes in Uganda. The parent study was powered to detect a difference in stroke outcomes between PWH and HIV- individuals, with a goal sample size of 300 participants (200 HIV- and 100 PWH). The study was terminated early, after enrolling 262 out of 300 planned participants due to insufficient funds to continue recruitment during COVID-19 related national restrictions. Because we enrolled HIV- participants only after a PWH with stroke in order to ensure appropriate matching, we had not yet completed enrollment of HIV- controls at the time of study termination.

For this analysis we compared sociodemographic, clinical stroke characteristics, traditional stroke risk factors, and psychosocial factors between PWH and HIV-sub-groups by using chi-squared testing or the Student's t-test where appropriate. We fitted logistic regression models, stratified by stroke type (ischemic vs. hemorrhagic), to estimate the correlation between known stroke risk factors and HIV serostatus at the time of stroke. We selected covariates for inclusion into the multivariable model if they had a p-value of ≤ 0.10 in univariable models and were established risk factors based on empirical data, such as depression and psychosocial risk factors. As such, adverse life events were not included. Furthermore, we considered it likely that adverse life events were in the causal pathway to psychosocial stress and depression and, therefore, did not include them for this either.

Ethical review

The study was approved by the research ethics committees of Mbarara University, MNH, Uganda National Council of Science and Technology, and Partners Healthcare. All participants or their primary caregivers provided written informed consent prior to enrollment.

Results

We enrolled 262 participants (105 PWH and 157 HIV-) between January 2018 and November 2020. The mean (SD) age was 55 (16) years, 52% (135/262) were men, and 63% (165/262) had primary school education or less (Table 1). Among PWH, 80% (78/105) were on ART for a median (IQR) duration of 5 years (1, 8), and the median (IQR) CD4 cell count was 214 (140, 337) cells/uL (Supplementary Table 2).

Among all patients with ischemic stroke (n=184), hypertension (53%), diabetes (22%), psychosocial stress (65%) and elevated low-density lipoprotein (LDL) > 100 mg/dl (51%) were common. PWH with ischemic stroke were more likely to; have an alcohol consumption history (51% vs. 29%, p=0.003), have hypertriglyceridemia (57% vs. 42%, p=0.043), report psychosocial stress at home or work in the last 12 months (75% vs. 58%, p=0.021), report the occurrence of an adverse life event in the last 12 months (24% vs. 51%, p=<0.001) and report depression in the last 12 months (16% vs. 5%, p=0.011) (Table 2). By contrast, HIV- persons with ischemic stroke were more likely to be older than 55 years of age (63% vs. 28%, p=<0.001) and to have hypertension (60% vs. 44%, p= 0.034), irregular heart rate (20% vs. 6%, p=0.009) and low fruit consumption (59% vs. 36%, p=0.002) (Table 2). In multivariable models, all these associations remained significant, except for hypertension. PWH with ischemic stroke had higher odds of hypertriglyceridemia (adjusted odds ratio (AOR) 1.63; 95% confidence interval (95% CI) 1.04–2.55, p=0.033), alcohol consumption (AOR 2.84; 95%CI 1.32–6.14, p=0.008), and depression (AOR 5.64; 95%CI 1.32–24.02, p= 0.019) while HIV- persons with ischemic stroke were more likely to be aged > 55 years (AOR 0.43; 95%CI 0.20–0.95, p= 0.037), have an irregular heart rhythm (AOR 0.31; 95%CI 0.10–0.98, p =0.047) and a diet low in fruit consumption (AOR 0.39; 95%CI 0.18–0.83, p=0.01) (Figure 1, Supplementary Table 3).

Among those with hemorrhagic stroke (n=78), hypertension (58%), psychosocial stress (74%) and low fruit consumption (54%) were common but did not differ between PWH and HIV- individuals in multivariable models (Figure 1).

Discussion

To our knowledge, this is among the largest studies evaluating stroke risk factors by HIV serostatus in the ART era in SSA. We found significant differences in the traditional and psychosocial risk factor profiles between PWH and HIV- individuals with ischemic stroke in Uganda. For example, PWH with ischemic stroke had higher odds of alcohol consumption, hypertriglyceridemia, and depression. By contrast HIV- persons with ischemic stroke were older, had a higher prevalence of arrhythmia, and had evidence to suggest poor dietary habits. These findings indicate that the optimal approach to ischemic stroke prevention in this region may differ based on HIV serostatus. Amongst those with hemorrhagic stroke, stroke risk factors occurred at similar rates, with hypertension being the most common, suggesting that a similar approach to hemorrhagic stroke prevention, such as detection and management of hypertension, could be effective in both groups. Several prior studies have established that hypertension is the most common cause of hemorrhagic stroke in SSA.[2,3]

Traditional cardiovascular risk factors viz., hypertension, diabetes, low HDL and smoking were prevalent in both PWH and HIV- persons with stroke and were similarly common in both groups with ischemic stroke. Unlike our data, prior studies in the region have shown that hypertension is more common in HIV- stroke persons when compared to PWH.[4,5] However, we analyzed ischemic stroke separately from hemorrhagic stroke and included a higher number of PWH, most of whom were on long-term ART. Therefore, our study might be more representative of risk factors for ischemic stroke among PWH in the ART era.

Despite being on ART for several years, PWH in our study had a median CD4 count (214 cells/μL) that is substantially lower than national estimates in Uganda (500 cells/μL).[6] This is consistent with prior studies indicating that a lower CD4 count might elevate stroke risk even in the absence of central nervous system opportunistic infections known to cause strokes, and further suggests that advanced disease and/or treatment failure might play a role in stroke pathogenesis, even in an era of widespread ART availability.[7,8] Therefore, efforts to ensure that PWH have access to early care, and that those who are on treatment maintain virologic suppression and optimal CD4 cell recovery may contribute to stroke prevention. These data would also support that PWH presenting with stroke should be evaluated for HIV treatment failure.

The median NIHSS score for all individuals in our cohort was 18 which is high. Unfortunately, it is not uncommon for patients with stroke presenting to hospitals in sub-Saharan Africa to have high NIHSS scores. This has been demonstrated in other regional studies from Tanzania[9] and Madagascar[10], among others. Our enrollment from tertiary referral facilities could partially explain this phenomenon as patients with severe strokes may be more likely to be referred from primary health centers to tertiary hospitals than patients with more mild strokes. Further, we included patients with intracerebral hemorrhage in the analysis for the NIHSS score which likely contributed to the higher median value because ICH patients tend to present with higher scores[11].

The major limitations of our study include incomplete matching due to early cessation of study enrollment, and the lack of longitudinal design to more formally address causal associations between all risk factors and stroke incidence. Incomplete matching meant that there were more male participants amongst PWH with stroke than in HIV- participants, and we did not reach our intended sample size of matching 2 controls to every case. This could lead to confounding, including with regard to sex-based risk factors such as alcohol consumption. However, we controlled for gender in the multivariate model. Notably, our finding on alcohol consumption is similar to what has been found in one recent study from Botswana.[5] We also did not collect data on adherence to ART or HIV viral load to determine their contributions to stroke. Psychosocial factors such as depression and stress screens can be prone to recall bias and imperfect validity, and should be interpreted with caution, considering these limitations. Lastly, our enrollment of participants at a tertiary referral facility could have led to referral bias as demonstrated by the high median NIHSS values at admission.

In summary, PWH with ischemic stroke in Uganda, unlike those with hemorrhagic stroke, exhibit a risk factor profile that differs from that of HIV- individuals. Most importantly, these data suggest interplay between HIV-associated risk factors, psychosocial risk factors and traditional risk factors in stroke risk that may require differentiated approaches to stroke prevention among PWH and HIV-uninfected adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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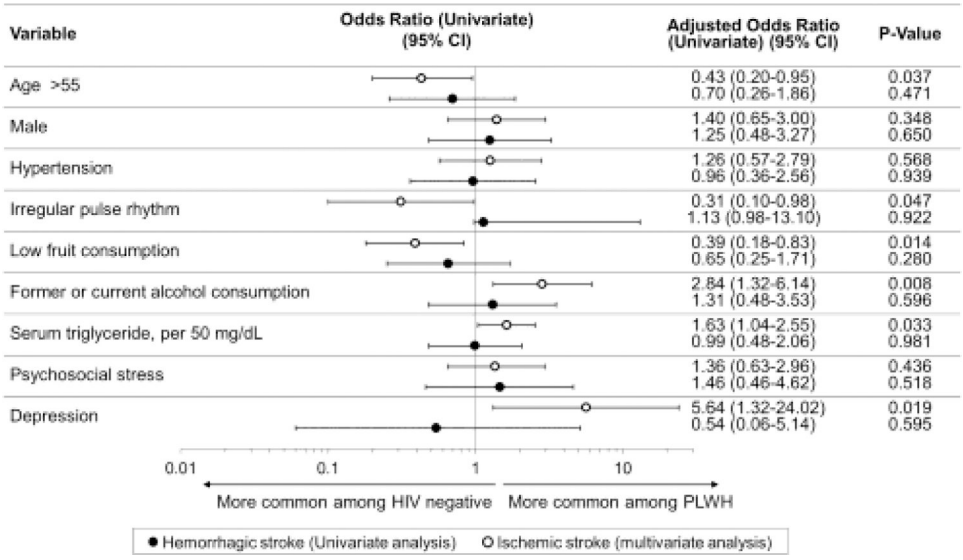

Figure 1:

Correlation between stroke risk factors and HIV serostatus in those with ischemic and hemorrhagic stroke in Uganda

The figure demonstrates that PWH with ischemic stroke had higher odds of hypertriglyceridemia, alcohol consumption and depression while HIV- persons with ischemic stroke were more likely to be aged > 55 years, have an irregular heart rhythm and a diet low in fruit consumption. Among all participants with hemorrhagic stroke there we no differences in stroke risk factors between PWH and HIV-. A multivariable model was performed in only those with ischemic stroke.

Table 1:

Socio-demographic and clinical characteristics by HIV serostatus

Variables	Total n = 262	HIV Negative n =157	PLWH n =105	*P*-value
Socio-demographic features				
Age, Mean (SD), years	55 (16)	59 (16)	48 (14)	**<0.001** *
Male sex, n (%)	135 (52)	72 (46)	63 (60)	**0.025** ^
Country region, n (%)				0.207^
Central	164 (63)	102 (65)	62 (59)	
Western	65 (25)	33 (21)	32 (31)	
Eastern	24 (9)	14 (9)	10 (10)	
Northern	7(3)	6 (4)	1 (1)	
Level of education, n (%)				0.156^
No formal education	57 (22)	43 (27)	14 (13)	
Primary school	108 (41)	64 (41)	44 (42)	
Secondary school	76 (29)	38 (24)	38 (36)	
Tertiary school	21 (8)	12 (8)	9 (9)	
Pre-hospital medications, n (%)				
Any antihypertensive	80 (57)	43 (27)	37 (35)	**0.001** ^
Aspirin	25 (10)	9 (6)	16 (15)	**0.010** ^
Any lipid lowering agent	10 (4)	4 (2)	6 (6)	0.197^
Stroke risk factors, n(%)				
Hypertension	144(55)	94(60)	50(48)	0.051 ^
Diabetes	45(17)	27(17)	18(17)	0.991 ^
Elevated LDL > 100 mg/dl	113(43)	64(41)	49(47)	0.344^
Psychosocial stress	177(68)	99(63)	78(74)	**0.032** ^
Stroke features				
Time from stroke onset to presentation, days, mean (SD)	3 (4)	3 (4)	3 (4)	0.513*
Ischemic stroke participants presenting within 4.5 hours, n (%)	9 (5)	1 (1)	8 (8)	**0.005** ^
Altered level of consciousness, n (%)	146 (56)	95 (61)	51 (49)	0.057^
Headache, n (%)	99 (38)	58 (37)	51 (49)	0.715^
History of fever, n (%)	43 (16)	20 (13)	23 (22)	0.052^
NIHSS at admission, mean (SD)	18 (7)	19 (8)	16 (7)	**0.010** *
Premorbid MRS of 0, n (%)	225 (86)	136 (87)	89 (85)	0.579^

* student t-test

^chi square

Table 2:

Prevalence of risk factors in individuals with stroke by HIV serostatus

	Ischemic stroke			Hemorrhagic stroke		
Variable, n (%)	**HIV negative, n = 103**	**PWH n = 81**	**P-Value***	**HIV negative n = 54**	**PWH n = 24**	**P-Value***
Age > 55 years	65 (63)	23 (28)	**0.000**	29 (54)	15 (63)	0.470
Male	48 (47)	51 (63)	**0.027**	24 (44)	12 (50)	0.650
Hypertension	62 (60)	36 (44)	**0.034**	32 (59)	14 (58)	0.939
Irregular pulse rhythm	20 (20)	5 (6)	**0.009**	2 (4)	1 (4)	0.922
Low fruit consumption	61 (59)	29 (36)	**0.002**	30 (56)	11 (46)	0.380
Former or current alcohol consumption	30 (29)	41 (51)	**0.003**	20 (37)	10 (42)	0.596
Serum triglyceride, >150 mg/dl	43 (42)	46 (57)	**0.043**	10 (19)	6 (25)	0.513
Diabetes	24 (23)	17 (21)	0.708	3 (6)	1 (4)	0.797
Stroke history	9 (9)	8 (10)	0.791	7 (13)	2 (8)	0.555
Former or current smoking	13 (13)	16 (20)	0.188	7 (13)	4 (17)	0.664
Low vegetables consumption	11 (11)	6 (8)	0.443	7 (13)	4 (17)	0.688
Serum LDL > 100 mg/dl	52 (51)	42 (52)	0.854	12 (22)	7 (29)	0.510
Serum HDL < 60 mg/dl	78 (76)	67 (83)	0.250	47 (87)	20 (83)	0.664
Psychosocial stress at home or work in the last 12 months	60(58)	61(75)	**0.021**	39(72)	19(79)	0.517
Depression in last 12 months	5 (5)	13 (16)	**0.011**	4 (7)	1 (4)	0.590
Adverse life events in the last 12 months	25 (24)	41 (51)	**0.000**	17 (32)	9 (38)	0.603
Physical activity levels in the last 12 months						
High	35 (34)	38 (47)		26 (48)	16 (67)	0.490
Moderate	26 (25)	20 (25)		13 (24)	5 (21)	
Low	12 (12)	6 (7)	0.313	5 (9)	1 (4)	
Unknown/Not sure	30 (29)	17 (21)		10 (19)	2 (8)	