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RESEARCH ARTICLE

Prevalence and Characteristics of HIV-Associated Stroke in a Tertiary Hospital Setting in South Africa

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Abstract

Background and Objectives

Antiretroviral treatment (ART) era HIV-associated stroke data from sub-Saharan Africa are limited. We determined the prevalence of HIV in patients presenting with acute symptomatic stroke and compared risk factors, clinical characteristics, and brain imaging with age-matched stroke patients without HIV.

Methods

We conducted a retrospective study of adults presenting with any type of stroke to Tygerberg Hospital in a 12-month period. Patients living with HIV (PLWH) and HIV-uninfected (HIV−) patients were matched based on age group (1:2 ratio). Patients were identified by keyword search, while HIV status was ascertained from laboratory data. Clinical and imaging data were extracted from medical records.

Results

Among 884 patients presenting with acute strokes, the minimum prevalence of HIV infection was 9.3% (95% CI: 7.4%–11.2%), with 496 patients (56.1%) with negative HIV status and 306 patients with unknown HIV status (34.6%). The mean age at presentation in PLWH was 46 (±11) years compared with 55 (±14) years in HIV− patients ($p < 0.001$). Smoking was less prevalent in PLWH with an adjusted relative risk ratio of RR = 0.58 (95% CI: 0.39–0.86). Concurrent infection was more prevalent in PLWH (25.6% vs 4.9%, $p \leq 0.001$) with an adjusted relative risk ratio of RR = 2.07 (95% CI: 1.49–2.84), largely in patients with a CD4 count <200 cells/μL. PLWH with higher CD4 counts (≥200 cells/μL, 51.3%) had more traditional risk factors and less concurrent infection. Among PLWH, 68.3% were on ART, and 39.3% of them had been started or restarted on ART within the past 6 months. Basal ganglia infarcts (35.6% vs 18.3%, $p = 0.014$) and multiple vascular territory involvement (25.4% vs 7.7%, $p = 0.002$) were more common in PLWH. Clinical presentation, ischemic stroke type, and in-hospital outcomes did not differ between the groups.

Discussion

Stroke patients with HIV were younger, had less traditional cardiovascular risk factors, and more concurrent infections than patients without HIV, especially those with a lower CD4 count. Recent ART initiation or reinitiation rates were high. Significant differences in CT brain imaging findings were seen. Understanding the multifactorial mechanisms underlying increased stroke risk, including associated infections and potential ART-associated immune reconstitution, is crucial and needs further study.

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Page 366

From the Divisions of Clinical Pharmacology (C.C., E.H.D., F.C.C.) and Neurology (N.B.), Department of Medicine, Division of Radiodiagnosis (R.D.P., S.O.H.), Department of Medical Imaging and Clinical Oncology, and Biostatistics Unit (T.M.E.), Division of Epidemiology and Biostatistics, Stellenbosch University, Cape Town Western Cape, South Africa; and Departments of Neurology and Medicine (Infectious Diseases) (F.C.C.), University of California, San Francisco.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

ART = antiretroviral treatment; **BP** = blood pressure; **CKD** = chronic kidney disease; **DM** = diabetes mellitus; **HIC** = high-income country; **LMIC** = lower-income and middle-income country; **PACS** = Picture Archiving and Communication System; **PLWH** = patients living with HIV; **SSA** = sub-Saharan Africa.

Stroke incidence in lower-income and middle-income countries (LMICs) such as sub-Saharan Africa (SSA), particularly in younger patient groups, is rising.[1] Two-thirds of the world's HIV population live in SSA, with South Africa having the greatest absolute number of HIV-infected individuals in the world.[2,3] In 2016, South Africa adopted the recommendation by the World Health Organization to initiate all patients living with HIV (PLWH) on antiretroviral treatment (ART) regardless of their $CD4^+$ count.[4] This approach resulted in approximately 5 million PLWH receiving ART of approximately 7 million PLWH in South Africa.[3] However, data on HIV-associated stroke in SSA, including South Africa, and especially in the ART era, is limited.[5-11]

Most research on HIV-associated stroke originates from high-income countries (HICs),[12-19] and patient characteristics may differ from those in LMICs. Differences in the median age and traditional cardiometabolic risk factor prevalence have been highlighted between PLWH and stroke patients without HIV (HIV−) from different income settings.[2] As PLWH age, their prevalence of traditional stroke risk factors increases with an accompanied elevation in the likelihood of stroke.[20-22] These risk factors include hypertension, dyslipidemia, diabetes mellitus (DM), obesity, smoking, coronary artery disease, and atrial fibrillation.[19] HIC data indicate that HIV is an independent risk factor for ischemic stroke and higher stroke rates are seen in PLWH, even after adjusting for known stroke risk factors.[2] The excess stroke risk that HIV infection confers may be greater in younger patients and women.[15,16] HIV-specific risk factors are advanced diseases with low CD4+ counts (<200 cells/μL), unsuppressed viral load, ART naivety, and potentially recent initiation of ART as part of a CNS immune reconstitution inflammatory syndrome (IRIS).[2,19,20]

The sudden onset of focal neurologic deficits is the most common presentation of stroke in both PLWH and HIV− patients.[19] However, less common features may present in HIV-associated stroke.[19] In PLWH, fever, seizures, and coexisting opportunistic infections are more common.[2] Stroke may be the first clinical manifestation of HIV infection in a large proportion of patients (studies found a range of 42%–57%).[2] There is paucity of data on the brain imaging findings in PLWH vs HIV− stroke patients from LMICs, with most of the data from HICs.[13,15,17,23,24] A systematic review indicated that ischemic stroke type was proportionally greater in PLWH when compared with their HIV− counterparts.[2] Recent SSA data indicate that stroke type (i.e., ischemic or hemorrhagic) does not differ in PLWH.[21,22,25] Regarding subtype, some studies showed greater small vessel infarcts or lacunar infarcts in PLWH compared with those in HIV- stroke patients.[21,25] A possible increased morbidity and mortality for HIV-associated stroke patients is still uncertain, with multiple studies finding dissimilar outcomes.[2,21,22,25-27]

In summary, while there has been greater ART access in the high-prevalence subtype C HIV population from South Africa, HIV-associated stroke prevalence data in the ART era are limited. Moreover, there is a paucity of updated information on differences in these patients with unadjusted age as a major confounder. Where studies have been performed, they are often small,[21] in specialist stroke units,[22] or have limited access to any imaging due to resource constraints.[20,22]

In this study, our primary aim was to determine the 12-month period prevalence and the age and sex distribution of HIV-associated stroke in Tygerberg Hospital, a tertiary hospital in Cape Town, South Africa. We secondarily aimed to compare differences in risk factors, clinical characteristics, and brain imaging features of PLWH with an age-stratified sample of HIV- patients presenting with stroke.

Method

Study Design and Setting

We conducted a retrospective study of hospital records of all adult patients presenting with stroke to Tygerberg Hospital in a 12-month period from January 1, 2019, to December 31, 2019. We further used a case-comparison design to compare PLWH with a sample of HIV- stroke patients. Tygerberg Hospital is the largest public sector tertiary hospital in Cape Town and second largest in South Africa. It provides service to more than 3.4 million people, chiefly vulnerable populations from densely populated low-income or rural communities. The Tygerberg Hospital catchment area treats a diverse population representing all cultural groups including Eastern Cape residents who travel to Cape Town for economic opportunities and medical care.

Participant Identification

We included adult patients (aged 18 years or older) who presented to Tygerberg Hospital with clinical or radiologic evidence of any type of stroke in 2019. Patients were identified using the Picture Archiving and Communication System (PACS). A key word search was performed on all CT brain imaging reports in the PACS for the year of 2019, compiled by the Tygerberg Division of Radiodiagnosis, using the following search terms: stroke, cerebral vascular accident, ischemic infarct, cerebral artery infarct, brainstem infarct, cerebellar infarct, hypertensive hemorrhage, hemorrhagic venous infarct,

cerebellar hemorrhage, hemorrhagic infarct, and hemorrhagic transformation of infarct.

To avoid missing potential patients, cases were also identified using the Clinicom patient administration system using stroke-specific *International Classification of Disease*-10 codes I60–I69 in 2019. Duplicate results were removed.

Identified patients were assessed for eligibility, and the diagnosis of stroke was established using relevant clinical information extracted from stored medical records on the Electronic Content Management System and laboratory results on the South African National Health Laboratory Service database. The first stroke of the year was counted in patients with repeated presentations within the period.

Patients were excluded if no clinical notes were available; if the presentation was due to stroke mimics, such as malignancy, seizure, brain abscesses, CNS toxoplasmosis, or CNS tuberculomas (but not excluding stroke in the setting of infection causing vascular dysfunction); if investigations found an alternative diagnosis to stroke; or if patients presented with any CNS or non-CNS trauma-related injuries (eTable 1, eTable 2, links.lww.com/WNL/C108).

Outcomes and Data Collected

Detailed clinical record data were abstracted for PLWH and a randomly selected age-stratified HIV- comparison group and entered on a standardized case report form on the REDCap database.[28] Risk factors were identified in physician discharge summaries, admission records, clinical notes, and laboratory results. Traditional risk factors collected were hypertension, DM type 1 or 2, dyslipidemia, cardiac conditions such as atrial fibrillation, cardiomyopathy, and valvular disease, obesity (when noted clinically), recent or current infection, recent or current cancer diagnosis, and a history of transient ischemic attacks or stroke events. Serious comorbidities that were associated with an increased risk were collected and grouped (such as ischemic heart disease, other peripheral cardiovascular diagnoses, chronic kidney disease [CKD], pregnancy-related conditions, and rheumatologic, neurologic, hematologic, respiratory, or endocrine diagnoses, or a combination thereof). Health-related behaviors that were collected included current history of smoking, alcohol use, and substance use.

In the South African public sector, hypertension, DM, and dyslipidemia are diagnosed as per the Adult Hospital Level Standard Treatment Guidelines and Essential Medicines List.[29] Patients were recorded as having a risk factor if it was clinically noted, measurements or diagnostic readings were documented, or special investigations provided evidence confirming the diagnosis. Controlled hypertension was defined therefore as a known hypertensive with blood pressure (BP) readings of less than 140/90 mm Hg after admission or less than 130/80 if DM or CKD present. Controlled DM was defined as an HbA1c value of <6.5%. Obesity was defined as any clinical note of raised body mass index (BMI), increased waist circumference, and increased central adiposity. Smoking, alcohol use, and substance use were collected in the same manner.

Stroke presentation features that were collected were grouped beforehand as follows: typical stroke features and less typical stroke features. Typical stroke features were recorded as focal weakness, focal sensory complaint, aphasia, neglect, homonymous hemianopia, and cerebellar dysfunction (such as vertigo, nystagmus, and ataxia). Less typical ischemic stroke features were altered mental status (Glasgow coma scale of 13/15 or less), progressive or stepwise neurologic deficit (over hours or days), seizures (not associated with epilepsy), and headache.[18] More than 1 feature could be noted per patient.

Based on radiologic description, stroke type was categorized as follows: ischemic, hemorrhagic, TIA, venous infarct, ischemic with hemorrhagic transformation, or unknown. It was noted whether a CT was performed. For each stroke type, the location of the stroke and documented vascular territory were recorded as per the CT brain report. Multiple locations could be selected per patient.

The virologic, immunologic, and ART status was collected for each PLWH. For HIV viral load, the laboratories use either the Abbott Alinity M HIV-1 Test or the Roche COBAS AmpliPrep/TaqMan HIV-1 Test, v2, which are dependent on the sample volume tested and have lower than detectable limits of either 20 or 100 RNA copies/mL. All values less than 100 RNA copies/mL were considered to be virally suppressed. We used an attributed value of one half of the lower limit of detection for those with undetectable viral load. Previous defaulting of treatment or poor adherence is the cessation of ART use by the patient for whatever reason.

In-hospital mortality was recorded for both groups. Hospital stay length was calculated using the date of admission and the date of discharge or date of death.

Statistical Considerations and Matching of Comparison Group

Data were analyzed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp, Armonk, NY) and Stata MP Statistical software: Release 17 (StataCorp LLC, College Station, TX). The calculation of the 12-month period prevalence of PLWH presenting to Tygerberg hospital with stroke in 2019 was determined using a simple proportion calculation from the entire eligible 2019 sample. From this sample, a subsample consisting of all PLWH and an age-stratified comparison group of HIV- patients in a ratio of 1:2 was randomly selected for further statistical analysis. The age-group matching process was as follows: PLWH and confirmed HIV- patients were subdivided into those younger than 45 years (PLWH, n = 39 [47.6%] and HIV-, n = 109 [22.0%]) and older than 45 years (PLWH, n = 43 [52.4%] and HIV-, n = 387 [78.0%]). We then selected a random sample of double the HIV- patients

from each age group. Therefore, 78 patients from the 109 young HIV- group (39:78 = 1:2) and 86 patients from the 387 old HIV- group (43:86 = 1:2) were selected. The PLWH group was also divided into immunologically severely compromised (CD4 count of <200 cells/μL) or not (CD4 count of ≥200 cells/μL). Certain continuous variables were categorized into clinical and statistically relevant groups for the purposes of statistical analysis and intervariable comparison. The Pearson χ^2 test or Fisher exact test was used for categorical variables and the Mann-Whitney test for continuous variables. Multivariable log binomial models were used to assess adjusted relative risks using covariates that met the 0.05 level of significance in the unadjusted analyses. Statistical significance was set at a p value of less than 0.05.

Standard Protocol Approvals, Registrations, and Ethical Approval

Ethical approval for the study and a waiver of consent were obtained from the Human Research Ethics Committee of the Faculty of Medicine and Health Sciences of Stellenbosch University (reference number: N20/07/075), and permission was obtained from the relevant hospital and Western Cape Health Department authorities.

Data Availability

Deidentified data will be made available by the primary author on reasonable request.

Results

Demographics

During 2019, 884 patients presented or were referred to Tygerberg Hospital with an acute stroke; 82 (9.3%) were HIV-positive, 496 (56.1%) were HIV-, and 306 (34.6%) were HIV unknown, resulting in an HIV prevalence of 9.3% (95% CI: 7.4%–11.2%) (Figure 1). Assuming the HIV unknown stroke group to have similar HIV prevalence to the Western Cape provincial HIV prevalence of 12.6% (95% CI: 9.7–16.1)[30] would result in a further 38 HIV-positive patients of 306 and a total of 118 stroke PLWH, resulting in an adjusted prevalence of 13.3% (95% CI: 11.1%–15.6%). The baseline characteristics are summarized in Table 1.

Risk Factors and Comorbidities

We compared our HIV-associated stroke patients (n = 82) with a group of randomly selected age-matched HIV- stroke patients (n = 164). Hypertension was more prevalent among the HIV- group (70.1% vs 53.7%, p = 0.011), especially known hypertensives who were poorly controlled (74.8% vs 52.3%, p = 0.006). However, newly diagnosed hypertension was more common in the PLWH group (31.8% vs 15.7%, p = 0.023). Dyslipidemia was also more prevalent among the HIV- group (29.9% vs 13.4%), p = 0.005). Conversely, multivariable log binomial models found recent or current infection (e.g., tuberculosis and syphilis) was twice as prevalent in PLWH with a risk ratio of 2.07 (95% CI: 1.49–2.84) (Table 1). Among health-related behaviors, smoking was less prevalent in PLWH with an adjusted relative risk of RR = 0.58 (95% CI: 0.39–0.86). The prevalence of obesity was more in the HIV- group but not statistically significant.

HIV-Specific Information

Of the 82 PLWH, 64 patients underwent a viral load measurement during stroke. Of them, 34 patients were virally suppressed (53.1%). The median viral load log was 1.70 (IQR 1.32–4.54). Comparing the virally suppressed patients with their unsuppressed counterparts, the only risk factor that differed between the 2 groups was current infection (virally suppressed, n = 6 [17.6%] vs n = 12 in the unsuppressed group [40%], p = 0.047). The median CD4 count during stroke was 205 (IQR 100–409) cells/μL with a median CD4 nadir of 155 (IQR 70–369) cells/μL. Patients with higher CD4 counts had more traditional risk factors for stroke (Table 2) despite similar mean age and sex.

Of the PLWH experiencing stroke, 68.3% were on ART during stroke, and 39.3% of them had been started or restarted on ART within the past 6 months, with a larger proportion in the lower CD4 group (64.0% vs 20.0%, p = 0.001). Previous ART poor adherence was also greater in the lower CD4 group (56.8% vs 31.4%, p = 0.031).

Key Features of Clinical Presentation

Table 3 summarizes the clinical features that the patients with stroke presented with. There were no significant differences in presentation between PLWH and HIV- patients. Patients with a lower CD4 count were more likely to present with altered mental status (44.7% vs 17.5%, p = 0.009).

Stroke Type and Radiologic Description

The stroke type and location comparison are summarized in Table 4. Ischemic stroke was the most common stroke type (66.3%), followed by hemorrhagic stroke (26.4%). For 3 patients in the HIV- group, the attending consultant decided against CT brain scan owing to the poor prognosis in these individuals.

PLWH had significantly more acute basal ganglia ischemic infarcts (35.6% vs 18.3%) and greater multiple vessel territory involvement (25.4% vs 7.7%). We did not find a significant difference between the lower and higher CD4 count groups.

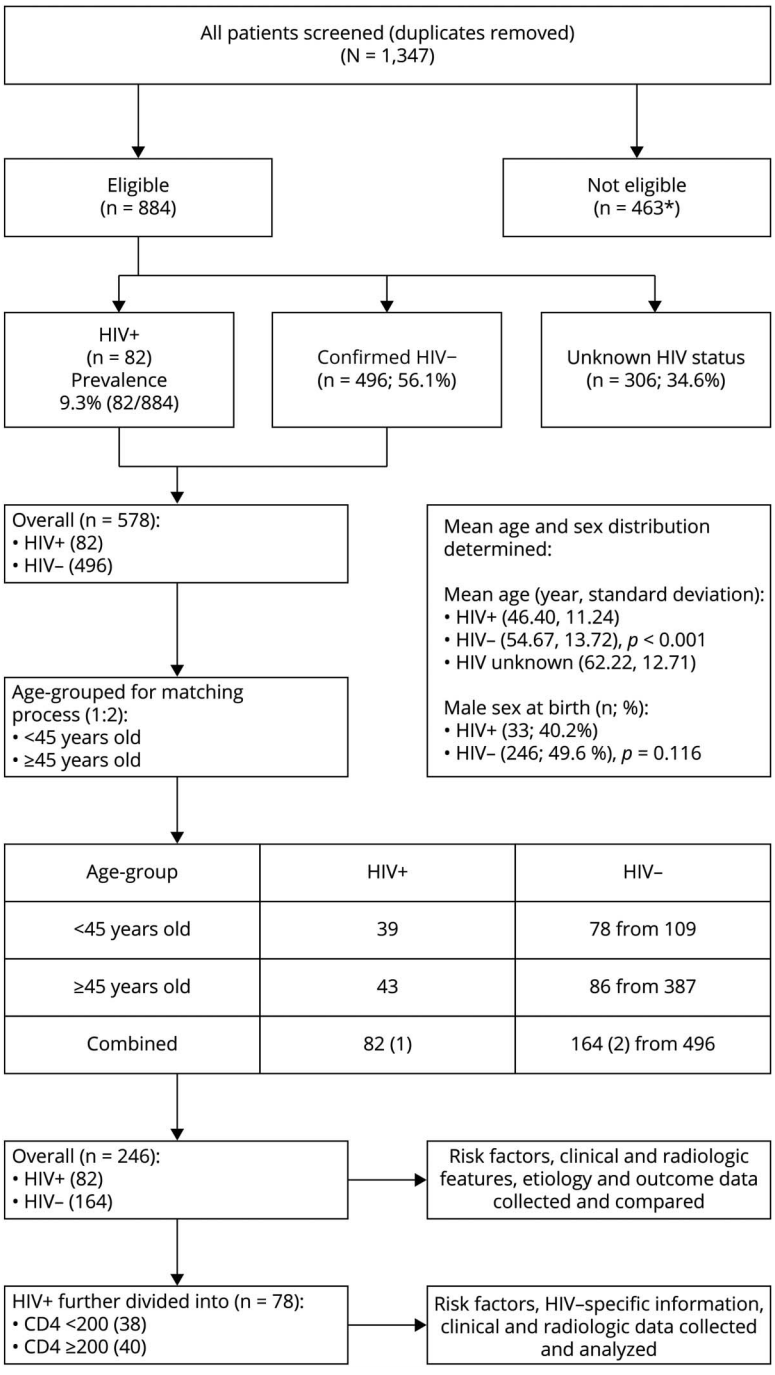
In-Hospital Mortality and Hospital Stay Length

We found no difference between the 2 groups regarding in-hospital mortality (Table 5). There was also no difference for hospital stay, whether one included only the living patients, only those who demised, or all patients.

Discussion

In this study of PLWH and HIV- patients presenting with acute stroke at a large tertiary hospital in Cape Town, South Africa, PLWH were nearly a decade younger. We found a

Figure 1 Diagram of the Selection of Patients for Study Inclusion and Age-Matching Process



Eligible patients (n = 884) were grouped as confirmed HIV-positive (HIV+, n = 82), confirmed HIV− (n = 496), and status unknown (n = 306). Status unknown consisted of patients who were either not tested or the HIV test was rejected by the laboratory for too little specimen or a separate sample not being provided. All patients in the abovementioned groups were involved to complete the primary objectives of prevalence and age and sex distribution. After this, we grouped the HIV+ and confirmed HIV- patients into 2 age groups: young (younger than 45 years) (HIV+, n = 39 [47.6%] and HIV-, n = 109 [22.0%]) and old (aged 45 year or older) (HIV+, n = 43 [52.4%] and HIV-, n = 387 [78.0%]). We then selected a random sample of double the HIV- patients from each age group. Therefore, we selected 78 patients from the 109 young HIV- group (39:78 = 1:2) and 86 patients from the 387 old HIV- group (43:86 = 1:2). The HIV+ group was further divided into immunologically severely compromised (CD4 count of <200 cells/μL) or not (CD4 count of ≥200 cells/μL). *ineligible patients delineated in supplemental tables (eTable 1 and eTable 2, links.lww.com/WNL/C108)

minimum HIV prevalence of 9.3% (95% CI: 7.4%–11.2%) in all patients with acute stroke in the setting of a provincial HIV prevalence of 12.6% (95% CI: 9.7%–16.1%).[30] Compared with age-matched HIV- patients presenting with acute stroke, PLWH had less traditional risk factors for stroke and were more likely to have a concurrent infection. This difference was more evident in patients with CD4 counts of <200 cells/μL. Ischemic strokes in PLWH were more likely to involve more than 1 vascular territory and the basal ganglia compared with those in HIV- patients with stroke. Our data add to the understanding of the evolving interplay of HIV infection and noncommunicable disease in an LMIC setting with a high prevalence of HIV in the ART era.

Our data echo the growing body of literature that PLWH experiencing stroke are younger than HIV- patients. The exact mechanism by which HIV leads to younger stroke is yet to be confirmed, but it is likely multifactorial. Macrophages are involved in the development of atherosclerosis, and the transmigration of HIV-infected macrophages and subsequent cytokine release leads to endothelial dysfunction, which may be

Table 1 Characteristics of HIV-Positive (HIV+) Compared With Age-Matched HIV-Negative (HIV−) Patients Presenting With Stroke at Tygerberg Hospital in 2019

Characteristics of age-stratified patients, n (%)	HIV+ (n = 82)	Age-matched HIV− (n = 164)	Overall (n = 246)	Crude *p* value	Adjusted *p* value	RR (95% CI)
Demographics						
Median age, y, (IQR)	46 (38–59)	46 (40–54)		0.517	0.493	
Male sex at birth	33 (40.2%)	77 (47.0%)		0.319		
Stroke risk factors						
Medical comorbidities						
Hypertension	44 (53.7%)	115 (70.1%)	159 (64.6%)	0.011	0.243	0.81 (0.57–1.15)
Diabetes mellitus	16 (19.5%)	31 (18.3%)	47 (19.1%)	0.909		
Dyslipidemia	11 (13.4%)	49 (29.9%)	60 (24.4%)	0.005	0.162	0.66 (0.36–1.18)
Obesity	4 (4.9%)	21 (12.8%)	25 (10.2%)	0.052		
Atrial fibrillation	2 (2.4%)	10 (6.1%)	12 (4.9%)	0.209		
Cardiac risk factors	3 (3.7%)	12 (7.3%)	15 (6.1%)	0.258		
Current infection	21 (25.6%)	8 (4.9%)	29 (11.8%)	<0.001	<0.001	2.07 (1.49–2.84)
TBM	7 (33.3%)	0 (0%)				
Disseminated TB	6 (28.6%)	0 (0%)				
Pulmonary TB	5 (23.8%)	3 (37.5%)				
Syphilis	4 (19.0%)	3 (37.5%)				
Cryptococcal meningitis	2 (9.5%)	0 (0%)				
Other infections	2 (9.5%)	2 (25%)				
Recent cancer diagnosis	0 (0.0%)	4 (2.4%)	4 (1.6%)	0.304		
Previous stroke or TIA	11 (13.4%)	25 (15.2%)	36 (14.6%)	0.702		
Other serious comorbidities[b]	11 (13.4%)	28 (17.1%)	39 (15.9%)	0.459		
Health-related behaviors						
Smoker	22 (26.8%)	85 (51.8%)	107 (43.5%)	<0.001	0.007	0.58 (0.39–0.86)
Alcohol use	12 (14.6%)	35 (21.3%)	47 (19.1%)	0.207		
Substance use[c]	8 (9.8%)	18 (11.0%)	26 (10.6%)	0.769		

Abbreviations: CKD = chronic kidney disease; IHD = ischemic heart disease; TB = tuberculosis; TBM = TB meningitis; RR = risk ratio.
[a]The mean age of the status unknown group was 62.22 (±12.71) years.
[b] IHD (n = 5), CKD (n = 5), rheumatological/vasculitides (n = 5), peripheral cardiovascular diagnoses (n = 3), pregnancy related (n = 3), neurologic (n = 6), hematologic (n = 6), respiratory (n = 4), endocrine (n = 3), combination (n = 3).
[c] Methamphetamine (n = 16), cannabis (n = 13), mandrax (methaqualone) (n = 10)—Note: Total does not equal 26 because patients could be polysubstance users.

responsible for accelerated atherosclerosis in PLWH.[18] Histopathologic postmortem findings have shown small-sized to medium-sized vessel preclinical atherosclerosis in HIV-infected male brains with no underlying opportunistic infections.[31] Specific viral protein polymorphisms in South Africa's Subtype C HIV-1 may facilitate viral replication within macrophages and have been associated with acute ischemic stroke.[32] Non-atherosclerotic intimal changes have also been described in the vessels of PLWH.[33] Coexisting infections also need to be considered. Stroke patients with HIV were more than double as likely to have a current infection. TB is especially prevalent in the Western Cape of South Africa,[34] syphilis remains an important cause of cerebral arteritis and stroke, and opportunistic viruses such as varicella-zoster virus, although not frequently tested in our setting, are implicated in vasculopathy and stroke. Multiple studies indicate that systemic infection may precipitate stroke.[35] The risk is greater in bacteremia but includes other viral infections. These non-CNS infections may trigger inflammation and thrombosis, and proposed viral-related mechanisms include platelet activation and aggregation, infection-triggered cardiac arrhythmias, and thrombosis induced by inflammation, dehydration, or endothelial dysfunction.[35] Underlying infection may serve as catalysts in an inflammatory pathway when initiating or reinitiating ART, as in

Table 2 Characteristics of PLWH Presenting With Stroke Stratified by CD4 Count

Characteristic, n (%) except where specified	CD4 <200 (n = 38)	CD4 ≥200 (n = 40)	Crude *p* value
Demographics			
Median age (IQR)	45 (41–54)	48 (40–55.50)	0.592
Male	17 (44.7%)	14 (35.0%)	0.380
Stroke risk factors			
Medical comorbidities			
Hypertension	14 (36.8%)	27 (67.5%)	0.007
Diabetes mellitus	6 (15.8%)	10 (25.0%)	0.314
Dyslipidemia	1 (2.6%)	9 (22.5%)	0.009
Obesity	0 (0%)	4 (10.0%)	0.045
Atrial fibrillation	2 (5.3%)	0 (0%)	0.234
Cardiac risk factors	0 (0%)	3 (7.5%)	0.241
Current infection	16 (42.1%)	5 (12.5%)	0.003
Previous stroke or TIA	11 (13.4%)	25 (15.2%)	0.702
Health-related behaviors			
Smoker	7 (18.4%)	14 (35.0%)	0.099
Alcohol use	5 (13.2%)	6 (15.0%)	0.815
Substance use	2 (5.3%)	5 (12.5%)	0.432
HIV-specific factors			
Virally suppressed	7 (22.6%)	26 (81.3%)	<0.001
ART status[a,b]	**CD4 <200 (n = 25)**	**CD4 ≥200 (n = 30)**	**Crude *p* value**
<6 mo since ART initiation	3 (12.0%)	2 (6.7%)	0.493
<6 mo since ART reinitiation after defaulting	13 (52.0%)	4 (13.3%)	0.002
On ART ≥6 mo	7 (28.0%)	23 (76.7%)	<0.001
Unknown regimen	2 (8.0%)	1 (3.3%)	0.585
Previously defaulted	21 (56.8%)	11 (31.4%)	0.031

[a] 38 (67.86%) of the 56 patients on tenofovir-emtricitabine-efavirenz (TEE), which was the first-line treatment in 2019; 8 patients (14.29%) on zidovudine-lamivudine-lopinavir/ritonavir, 7 patients (12.50%) on abacavir-lamivudine-efavirenz, and 1 (1.79%) patient on tenofovir-emtricitabine-atazanavir, for 2 patients (3.57%), the regimen was unknown.
[b] Note that 1 patient was not included in table because CD4 count was not known.

IRIS. Patients with a lower CD4 count are much more predisposed to opportunistic infections.[36] It is of importance that the risk of IRIS is notably higher in patients with a lower starting CD4 count.[37]

There is an increasing burden of cardiometabolic and behavioral risk factors as PLWH grow older. Our data suggest that these risk factors are particularly important in patients whose HIV disease is well-controlled. Stroke patients with HIV were almost half as likely to be smokers. Hypertension and dyslipidemia were significantly less prevalent in the PLWH group, although multivariable analysis found that this significance may have been because of the conferred risk of smoking. This may reflect the established findings of HIV as a separate risk factor for stroke, especially in patients younger than 45 years.[17] It is of interest that patients with a higher CD4 count (≥200 cells/μL) had a greater prevalence of traditional risk factors in comparison with their immunologically compromised counterparts, even with similar age and sex distributions. This mirrored the differences of the PLWH group overall to the HIV- group. Those with a higher CD4 count may still have an underlying HIV-associated vasculopathy, which, when combined with traditional risk factors, compounds their risk of stroke and results in a younger age of stroke incidence. In particular, hypertension was the most prevalent risk factor overall, and a poor control in known hypertensives was greater in the HIV- group. However, newly diagnosed hypertension was more common in the PLWH group. This may likely be due to the known phenomenon of an acute rise in BP during stroke, partly due to a sympathetic reaction, and the possibility that attending clinicians noted a diagnosis of hypertension in the setting of an acute stroke without confirmation at a later stage. Alternatively, the explanation may be that PLWH are presenting sooner with complications in the course of developing hypertensive disease.

There are also the potential metabolic side effects of ART to consider. The lipid-deranging effects of protease inhibitors have been long-known. More recently, the ADVANCE study conducted in South Africa randomized ART-naïve participants to standard doses of dolutegravir or efavirenz and combined with other antiretrovirals, showed significant weight gain in the dolutegravir arms.[38] In our study, most of the patients were on an efavirenz-containing regimen. Intriguingly, further analysis of the ADVANCE data showed greater weight gain in women and in the efavirenz extensive CYP2B6 metabolizer genotype.[39] Obesity as a major risk factor for noncommunicable disease, particularly in females, is a growing concern in SSA. On the contrary, slow metabolizers of efavirenz had impaired weight gain, likely due to concentration-dependent mitochondrial toxicity and impaired adipocyte differentiation. The presence of mitochondria in all cells, including those of the CNS, and the implications of their dysfunction is a potential factor to consider in stroke risk and outcome.[40]

Concurrent infection was more prevalent in the PLWH group. This was largely driven by those with a CD4 count of <200 cells/μL, who were also less likely to be virally suppressed. It has been established that persistent HIV viremia leads to chronic inflammation that increases stroke risk.[36] The possibility exists that traditional risk factors leading to stroke were less likely to be documented in situations where other priorities such as an opportunistic infection requiring

Table 3 Stroke Presentation of HIV-Positive (HIV+) Compared With Age-Matched HIV-Negative (HIV-) Patients

Characteristic, n (%) except where specified	HIV+ (n = 82)	Age-matched HIV− (n = 164)	Overall (n = 246)	Crude *p* value
Typical stroke features				
Motor deficit	71 (86.6%)	131 (79.9%)	202 (82.1%)	0.196
Sensory deficit	9 (11.0%)	20 (12.2%)	29 (11.8%)	0.780
Homonymous hemianopia	3 (3.7%)	4 (2.4%)	7 (2.8%)	0.689
Aphasia	21 (25.6%)	29 (17.7%)	50 (20.3%)	0.145
Visuospatial neglect	3 (3.7%)	11 (6.7%)	14 (5.7%)	0.331
Cerebellar dysfunction[a]	6 (7.3%)	12 (7.3%)	18 (7.3%)	1.000
Less typical stroke features				
Altered mental status	25 (30.5%)	50 (30.5%)	75 (30.5%)	1.000
Progressive or stepwise neurologic deficit	4 (4.9%)	1 (0.6%)	5 (2.0%)	0.044
Seizures	5 (6.1%)	12 (7.3%)	17 (6.9%)	0.722
Headache	12 (14.6%)	31 (18.9%)	43 (17.5%)	0.406
HIV+ only characteristic, n (%) except where specified	**CD4 <200 (n = 38)**	**CD4 ≥200 (n = 40)**		**crude *p* value**
Less typical stroke features				
Altered mental status	17 (44.7%)	7 (17.5%)		0.009
Progressive or stepwise neurologic deficit	3 (7.9%)	1 (2.5%)		0.280
Seizures	3 (7.9%)	1 (2.5%)		0.280
Headache	6 (15.8%)	5 (12.5%)		0.677

[a] Vertigo, ataxia, and nystagmus.

treatment may have been at the forefront. Conversely, it is feasible that the underlying mechanisms of stroke in patients with higher CD4 counts of ≥200 cells/μL are more comparable with that of patients without HIV.

We found many patients were initiated or reinitiated on ART within 6 months before stroke and an overall high rate of previous defaulting of ART mostly in patients who had a lower CD4 count. Lack of adherence has been associated with biomarkers of chronic inflammation and has been implicated to increase the risk of non-CVD mortality in PLWH, even in those with virologic suppression.[41] Two Malawian studies have hypothesized potential immune reconstitution as a reason for stroke in the period near ART initiation: the first found 20% (n = 12) of patients with an adjusted OR for stroke of 15.6,[20] and the second found 25% (n = 16 of 64) of patients with stroke within 6 months of ART initiation.[33] Our data may support this increased stroke risk because of possible immune reconstitution and inflammation activation, with many of those initiating or reinitiating ART in the lower CD4 group.

We found that the clinical presentation of PLWH with stroke does not differ significantly from that of an HIV- patient. The immunologically compromised group was more likely to present with altered mental status, which may reflect the neurotropic nature of HIV itself, a greater risk of delirium in these patients, a consequence of another underlying infection, or a marker of underlying HIV-associated neurocognitive disorder. The location of strokes differed minimally between the 2 groups, except PLWH had more basal ganglia infarcts and more strokes involving multiple vascular territories. Multifocal strokes may suggest a vasculitic, hypercoagulable, or cardioembolic process. The etiology for this finding was not detected in this study. It is of interesting that both lower and higher CD4 categories had brain imaging findings of multifocality and basal ganglia predominance. An underlying vasculopathy may be present independent of the degree of immunosuppression or virologic status.

Overall, our findings are in line with evidence from higher income countries and contribute to the growing literature in LMICs that patients with HIV-associated stroke are younger and have less traditional risk factors present than HIV- patients with stroke.[17,19,21,22,25,27] A Zambian retrospective study also identified hypertension as the predominant risk factor in both PLWH and HIV- stroke patients, with significantly greater prevalence in HIV- patients.[27] Contrary to our findings, the reported study did not show a statistical difference between other risk factors such as dyslipidemia and

Table 4 Stroke Type and Location of HIV-Positive (HIV+) Compared With Age-Matched HIV-Negative (HIV-) Patients

Characteristic, n (%) except where specified	HIV+ (n = 82)	Age-matched HIV- (n = 164)	Overall (n = 246)	Crude *p* value
Stroke type	82	164	246	0.499
Ischemic	59 (72.0%)	104 (63.4%)	163 (66.3%)	0.182
Hemorrhagic	17 (20.7%)	48 (29.3%)	65 (26.4%)	0.152
Other[a]	6 (7.3%)	12 (7.3%)	18 (7.3%)	1.000
CT performed	82 (100.0%)	161 (98.2%)	243 (98.8%)	0.553
Acute ischemic stroke	**HIV+ (n = 59)**	**Age-matched HIV− (n = 104)**	**Overall (n = 163)**	**Crude *p* value**
Location				
Cerebral cortex and combined white matter tracts[b]	42 (71.2%)	66 (63.5%)	108 (66.3%)	0.316
Brainstem	3 (5.1%)	9 (8.7%)	12 (7.4%)	0.402
Basal ganglia	21 (35.6%)	19 (18.3%)	40 (24.5%)	0.014
Cerebellum	5 (8.5%)	5 (4.8%)	10 (6.1%)	0.348
>1 acute focal lesion	10 (16.9%)	10 (9.6%)	20 (12.3%)	0.170
Unknown/no evidence of acute stroke[c]	8 (13.6%)	23 (22.1%)	31 (19.0%)	0.181
Vascular territory				
Single vascular territory[d]	34 (57.6%)	67 (64.4%)	101 (62.0%)	0.390
>1 vascular territory involved	15 (25.4%)	8 (7.7%)	23 (14.1%)	0.002
Unknown[e]	10 (16.9%)	29 (27.9%)	39 (23.9%)	0.116
Acute hemorrhagic stroke	**(HIV+ n = 17)**	**(Age-matched HIV− n = 48)**	**(Overall n = 65)**	**Crude *p* value**
Location				
Parenchymal[f]	12 (70.6%)	28 (58.3%)	40 (61.5%)	0.372
Intracerebral/lobar	6 (50.0%)	7 (25.0%)	13 (32.5%)	0.122
Basal ganglia	4 (33.3%)	17 (60.7%)	21 (52.5%)	0.112
Other[g]	2 (11.8%)	6 (12.5%)	8 (12.3%)	0.937
Subarachnoid	9 (52.9%)	28 (58.3%)	37 (56.9%)	0.700
Other[h]	6 (35.3%)	6 (12.5%)	12 (18.5%)	0.037
HIV+ only characteristic, n (%) except where specified	**CD4 <200 (n = 38)**	**CD4 ≥200 (n = 40)**	**Overall n = 78**	**Crude *p* value**
Stroke type				
Ischemic	27 (71.1%)	31 (77.5%)	58 (74.4%)	0.515
Hemorrhagic	7 (18.4%)	7 (17.5%)	14 (17.9%)	0.916
Other[a]	4 (10.5%)	2 (5.0%)	6 (7.7%)	0.425
Acute ischemic stroke	**(HIV+ n = 27)**	**(Age-matched HIV− n = 31)**	**(Overall n = 58)**	**Crude *p* value**
Location				
Basal ganglia	9 (33.3%)	11 (35.5%)	20 (34.5%)	0.864
Vascular territory				

Continued

Table 4 Stroke Type and Location of HIV-Positive (HIV+) Compared With Age-Matched HIV-Negative (HIV-) Patients *(continued)*

Characteristic, n (%) except where specified	HIV+ (n = 82)	Age-matched HIV- (n = 164)	Overall (n = 246)	Crude *p* value
>1 vascular territory involved	7 (25.9%)	8 (25.8%)	15 (25.9%)	0.992

ACA: anterior cerebral artery; MCA: middle cerebral artery; PCA: posterior cerebral artery.
[a] Ischemic with hemorrhagic transformation, venous infarct, TIA.
[b] Subcortical; Centrum semi ovale; Corona radiata; Internal capsule; Corpus callosum; External capsule; Periventricular white matter; Deep white matter not defined (not the sum of its parts—if a patient had more than 1 of the abovementioned involved, counted as 1).
[c] Often either hyperacute, in which a CT brain may not detect changes, or the lesion was too early or small for CT detection.
[d] Includes MCA, ACA, PCA, and vertebrobasilar artery and branches (vertebral, posterior and anterior inferior cerebellar, basilar, superior cerebellar, and pontine arteries).
[e] Repeat CT brains are not frequently available for comparison to confirm vascular territory or stroke location if not evident in initial scan.
[f] Parenchymal hemorrhage could be in greater than 1 parenchymal location per patient.
[g] Thalamic, brainstem.
[h] Nontraumatic subdural hemorrhage with acute clinical presentation, supraclinoid internal carotid artery–ruptured aneurysm.

smoking, although they did note a significant limitation with not having electronic medical records in their in-patient neurology facility. Our findings are in agreement with a recent South African retrospective study with similar resources to ours that a greater prevalence of hypertension and dyslipidemia existed in HIV– stroke patients.[21] Our methodology allowed comparison between similar age groups because age difference was a confounding factor present in other studies that compared risk factors. Despite limited resources, we have reliable laboratory, pharmacy, and radiography data and were able to characterize HIV-specific patient characteristics and ART data well.

Our study had a number of limitations. Tygerberg Hospital is a large referral hospital, and it is possible that minor strokes may have been managed at peripheral clinics or hospitals. Sociogeographic patterns of stroke and HIV exist that may not be accounted for.[42] Furthermore, our prevalence result may have been a conservative estimate by using all eligible patients in the calculation and not only known HIV status participants. This may have led to an underestimation of our HIV prevalence, which was lower than the baseline HIV prevalence in the Western Cape of South Africa.[30] Assuming provincial prevalence in the unknown group, the adjusted prevalence was 13.3% (95% CI: 11.1%–15.6%). However, it is plausible that those in whom the HIV status was not known were more likely to be HIV negative. For example, low clinical suspicion may have precluded testing, among other possibilities. Hence, the conservative calculation may be more representative of the true prevalence. We did not match our comparison group for sex, and although the difference did not prove significant, this may have had an effect. We were unable to perform multivariable analysis to assess risk ratios stratified by $CD4^+$ count (Table 2) because insufficient events summarized in Table 2 beget a high likelihood of type 2 errors. Our study design was retrospective, and our data quality was dependent on the quality of routine clinical data. For example, raised BMI was noted clinically, which is likely an underestimate of the true prevalence of this risk factor. Furthermore, 7-day blood pressure values or new antihypertensive drug initiation on discharge are useful parameters to confirm newly diagnosed hypertension, but could not be reliably assessed retrospectively. In our resource-limited setting, more expensive workups are often deferred. Our center is a large referral hospital that is frequently operating at maximum capacity, and patients referred for CT scans are often seen and discharged within the same day for further workup or step-down management at the referring facility. This has implications for the in-hospital mortality and hospital stay length findings; these were not significantly different between the 2 groups, which agrees with prospective studies in Cameroon and Botswana.[25,26] However, others have shown worse outcomes in PLWH hospitalized with stroke.[22,43]

Table 5 In-Hospital Mortality and Hospital Stay Length of HIV-Positive (HIV+) Compared With HIV-Negative (HIV−) Patients

Characteristic, n (%) except where specified	HIV+ (n = 82)	Age-matched HIV− (n = 164)	Overall (n = 246)	Crude *p* value
In-hospital mortality	13 (15.9%)	17 (10.4%)	30 (12.2%)	0.215
Hospital stay length in d (median, IQR)			Mann-Whitney *U* Test asymptotic (2-sided)	
Only living patients (n = 216)	4 (2–9)	5 (2–10)	0.479	
Deceased patients (n = 30)	4 (0–10)	2 (0–6)	0.680	
All patients (n = 246)	4 (1–9)	5 (1.5–10)	0.624	

Potential future research could focus on assessing the risk factors in a prospective study that are more difficult to ascertain retrospectively, namely physical inactivity; waist-to-hip ratio, calculated specific BMI; diet; psychosocial stress or depression; ratio of apolipoproteins B to A1; and air pollution exposure.[44] In addition, the level of defaulting and reinitiation of ART we found was concerning, and the potential association between immune reconstitution and stroke should be further investigated.

In conclusion, we found a minimum prevalence of 9.3% of HIV in patients presenting in 2019 with acute stroke in Tygerberg Hospital. Stroke patients with HIV were younger and when age-matched, had less traditional cardiovascular risk factors and more concurrent infections than patients without HIV, especially those with a lower CD4 count. PLWH who were well-controlled on ART with higher CD4 counts have characteristics that were more comparable with the HIV- group, except for radiologic imaging findings. ART has transformed HIV into a chronic disease, with stroke as a serious complication of the interplay between cardiovascular risk factors and underlying HIV infection in an aging PLWH population. Understanding the multifactorial mechanisms underlying increased stroke risk, including associated infections and potential ART-associated immune reconstitution, is crucial and needs further study. The implications of HIV and the importance of control by consistent ART in these patients warrants consideration by clinicians and policy makers in stroke care in SSA, including South Africa.

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