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Stroke in HIV-infected individuals in sub-Saharan Africa (SSA): A systematic review

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Abstract

Background—HIV infection is associated with worse outcomes after stroke, but this association is less well described in sub-Saharan Africa (SSA). We reviewed literature on stroke among people living with HIV (PLWH) in SSA.

Methods—We systematically reviewed published literature for original clinical stroke studies conducted in SSA that included PLWH. We included studies that reported data on presenting characteristics, risk factors, and/or outcomes after stroke.

Results—Sixteen studies (N=477) met inclusion criteria. At the time of stroke presentation, PLWH had a median age ranging from 32 to 43 years. Subjects had low CD4 counts (median CD4, 108 – 225 cells/μl), and most were antiretroviral therapy naïve. Fever, seizures and concurrent opportunistic infections were common at presentation. Ischemic stroke accounted for up to 96% of strokes, which were mostly located in the anterior circulation territory. In studies comparing PLWH with HIV-uninfected individuals, PLWH had more frequent coagulopathy, greater stroke severity, (72% vs 36% NIHSS >13, P=0.02), longer hospital length of stay (30.5 vs <10 days) and a higher thirty-day mortality rate (23% vs 10.5%, P=0.007).

Conclusion—Stroke in PLWH in SSA occurs at a young age, in those with advanced disease, and is associated with worse outcomes than in HIV-uninfected comparators. Stroke in young individuals in the region should prompt HIV testing, and ongoing efforts to promote early ART initiation might also help decrease stroke incidence, morbidity and mortality in the region.

Keywords

Stroke; HIV infection; sub-Saharan Africa

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Introduction

The widespread use of combined antiretroviral therapy (cART) has led to a decrease in morbidity and mortality from AIDS and significantly increased the life expectancy for those infected [1–3]. Improvement in life expectancy has shifted health priorities for people living with HIV (PLWH) from treatment and prevention of opportunistic infections to include focus on non-AIDS related conditions [4,5]. HIV infection has been demonstrated to significantly and independently increase the risk of stroke [6–9]. Several mechanisms for this relationship have been proposed, including HIV-related intra- and extra-cranial vasculopathy, HIV induced cardiomyopathy, HIV-induced coagulopathy, and opportunistic infection-associated vasculitis [10,11]. Among PLWH on ART, both the inflammation and immune activation associated with chronic HIV-infection and direct effects of antiretroviral therapy (ART) are hypothesized to contribute to stroke pathogenesis [5].

Although over two-thirds of the world's population of PLWH live in sub-Saharan Africa (SSA) [12,13], less is known about the contributions of HIV infection to stroke risk and stroke outcomes in the region. The impact of HIV on stroke risk in SSA is particularly important due to elevated stroke risk in the general population in this region [14]. Moreover, extrapolation of data from North America and Europe may not be valid due to differences in the environment, behaviors, and genetics between these populations. For example, intravenous drug abuse, which is prevalent among HIV-infected stroke patients in the Western world, is rare in Africa [15]. Additionally, there are important differences in the healthcare infrastructure for stroke care in the developed world, and this is likely to affect stroke outcomes [16–18].

This review sought to synthesize available literature on the risk factors, clinical presentation, and outcomes of stroke among PLWH in SSA. Our goals were to: 1) offer preliminary guidance to clinicians and public health programs in SSA on the evaluation and follow up of PLWH with stroke and 2) identify gaps and make recommendations to inform research priorities for stroke prevention and treatment in PLWH.

Methods

Search and screening strategy

In this review, we used the PRISMA statement as a guide. We searched the following electronic databases: PubMed, Scopus (MEDLINE and EMBASE), Google Scholar, Global Health, and The Cochrane Library for studies describing HIV and stroke in sub-Saharan Africa. Full details of our search terms are available in the Supplementary Appendix. We searched without any language restrictions and our search was last updated on 31st October 2016. One manuscript was translated into English using Google Translate after we failed to get in touch with the author [19]. We screened abstracts of all returned articles for inclusion criteria. To promote reliability and validity of the screening process, the first 100 abstracts/papers were screened by two reviewers (AA and JC) and any discrepancies discussed. All further reviews were done independently by AA. The study is registered with the PROSPERO study registry (no. CRD42017050741).

Criteria for selection

Other than the case reports, we used the following inclusion criteria to identify studies for further review: 1) At least 10 participants (or 20% of the total participants) with both HIV infection and a stroke; 2) description of clinical presentation at the time of stroke, risk factors for, and/or outcomes after stroke among PLWH; 3) at least 50% of observed stroke in PLWH confirmed by brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]); 4) study subjects were ≥18 years old; and 4) the study included original data (i.e. not a review or opinion piece). Thus we also excluded incidence and prevalence studies that had no clear description of patient characteristics, risk factor and/or outcomes.

Data Abstraction

For each included study, we abstracted and summarized data for each of the following categories; (i) clinical characteristics, (ii) traditional cardiovascular and HIV specific risk factors, (iii) outcomes (mortality and neurological function). Data were abstracted into a pre-specified Microsoft Excel spreadsheet (Redmond, Washington, United States). We used standard data summarization techniques to record each of the characteristics in the three domains of interest.

Study bias

1. All studies meeting inclusion criteria were included in the systematic review. We used the Newcastle Ottawa Scale (NOS)[20] to assess the quality of all studies included in the review, apart from the case reports (Table 6).

Results

Our initial PubMed search yielded 140 papers. We excluded 118 papers after review of the abstracts and read the remaining 22 full-length manuscripts. We further excluded eight studies after review of the manuscripts. Our final analysis included 14 manuscripts from the initial PubMed search and 2 additional, non-duplicative studies identified from the other databases following a similar search strategy (Fig 1). Most of the studies were conducted in South and West Africa (Table 1) and involved patients who were ART naïve (Table 2).

Clinical characteristics of stroke in HIV infected persons

Table 2 summarizes findings from all studies describing clinical characteristics of PLWH with stroke in SSA. All of the studies were hospital based, and conducted in patients presenting with acute stroke syndromes. HIV-infected stroke patients in SSA are predominantly young, with median age ranging from 32 to 43 years [10,11,19,21,22]. There was a slight male predominance, with most studies reporting a male:female sex ratio in the range of 0.5–1.5:1.0 [10,19,22,23].

Neurological stroke syndromes among PLWH were comparable to those frequently seen in the general population, including isolated hemiparesis, hemiparesis with hemisensory loss, hemianopia, and aphasia [10,24]. Stroke severity was reported in two studies and showed that PLWH presented with moderate to severe stroke. About 63.1% of PLWH and stroke had a NIHSS >12 in one study and up to 77% of PLWH had NIHSS >13 in another. [19,21]. A

majority had ischemic stroke at presentation with most of the studies reporting rates between 80–96% [10,11,21,22,25]. Sub arachnoid hemorrhage in association with intracranial dissection was reported in two case studies [26,27]. Among ischemic strokes, the anterior circulation was the most frequently affected territory (82 to 94% of cases) [10,21,24,25]. Only one study reported a low rate of ischemic stroke of 67% [19]. Of the two studies that categorized ischemic strokes into subtypes using the Oxfordshire Community Stroke Project (OCSP) classification, partial anterior circulation strokes were the most common subtype (51–70%) followed by lacunar strokes (20–22%), and posterior circulation strokes (6–11%) [11,21].

HIV specific risk factors for stroke

HIV-infected stroke patients tended to present with advanced HIV disease. Median CD4 counts at presentation ranged from 108–214 cells/μl [19,23,25]. Historically, and consistent with trends in ART distribution in the region, most patients were ART-naïve at the time of presentation. Aside from one study in the Democratic Republic of the Congo, in which ART usage was reported in all observed individuals, most studies found ART was use in less than 50% of stroke patients at the time of presentation [10,11,19]. In fact, stroke was the first clinical manifestation of HIV infection in a large proportion of patients, ranging from 42% to 57% [10,11].

Seizures and fevers occurred frequently among PLWH with stroke in SSA, and may denote recent or concurrent HIV-associated opportunistic infections [10,19]. The proportion of PLWH and stroke with concurrent opportunistic infections ranged from 23 to 55% [10,11,28]. Overall, neurological opportunistic illnesses that were commonly seen in association with stroke included meningitis (tuberculous, cryptococcal, pyogenic, viral) meningovascular syphilis and varicella zoster vasculitis [10,24,29]. Non-neurological opportunistic infections were also frequently reported and included pulmonary tuberculosis, varicella zoster ophthalmicus, pneumocystis pneumonia, and Kaposi's sarcoma thus reflecting presence of advanced HIV infection in PLWH [10,11,24]. Furthermore, a comprehensive study of young individuals (age < 46 years) with ischemic stroke, reported meningitis as the most common risk factor associated with stroke, occurring in 28% (18/64) of individuals [11].

Only one study identified by our search estimated the contribution of HIV infection to stroke in sub-Saharan Africa. A case-control study from Malawi (n=723) compared hospital-based stroke cases with matched population-based non stroke controls and found that HIV infection was associated with an increased odds of stroke (adjusted odds ratio [aOR] 3.28 CI [2.05–5.25]) [30]. HIV accounted for the second highest population attributable fraction (15%) for stroke after hypertension (46%), although this varied by age. Moreover, associations were noted between lower CD4 count, shorter duration of ART initiation and increased odds of stroke. For example PLWH with CD4 count <200 had approximately 13 times higher odds of stroke compared with individual with CD4 count>500. PLWH in the early phase of ART initiation (within 6 months) were also found to have higher stroke risk (aOR 15.6 CI [4.21–46.6]), compared with HIV-uninfected individuals and, even, when compared to PLWH who were ART naïve (aOR 4.63 CI [1.06–20.1]).

Other HIV-related risk factors for stroke that were assessed included hypercoagulability and vasculopathy. The prevalence of markers of abnormal coagulation among PLWH was

variable, ranging from 10 to 57% [10,11,31]. In comparison, markers of abnormal coagulation were significantly higher in PLWH compared to those in HIV-uninfected patients with stroke [10,11]. The most common coagulopathies were deficiency in protein C, protein S, and the presence of antiphospholipid antibodies. Other reported abnormalities of coagulation included high von Willebrand factor (vWF), low ADAMTS13, positive circulating immune complexes, disseminated intravascular coagulation, and thrombocytopenia [10,32,33]. VWF and ADAM TS 13 were further found to be significantly abnormal in PLWH with stroke compared to PLWH without stroke [33].

A number of studies described cerebral vessel angiography results of stroke patients and reported a mixture of findings ranging from idiopathic HIV associated vasculopathy, atheromatous plaques, vasculitides, and dissection of the vessel wall [10,11,24,31]. Some of the studies compared the prevalence of any of these vasculopathies among PLWH with stroke and HIV uninfected controls by employing cerebral angiography and post-mortem histological analysis and found similar rates of the abnormal findings in PLWH and HIV-uninfected controls with prevalence estimates ranging from 20 to 33% (Supplementary Table S1), [10,11,24,31] although one study reported a significantly higher prevalence of intracranial large vessel vasculopathy in the PLWH subgroup [31,34]. Some case reports however, have demonstrated vessel characteristics consistent with idiopathic vasculopathy attributable to HIV infection itself [27,35,36]. In one case report, postmortem histological findings were consistent with those of a primary HIV vasculopathy with arterial fusiform dilatation and thrombotic occlusion [35].

In the published literature, cardioembolism occurs in PLWH at similar rates as compared to the general population. Echocardiographic evaluations for features of cardioembolic phenomena in PLWH report abnormal findings in about 9–14% [10,35]. One study, directly comparing echocardiography between PLWH with stroke and HIV-uninfected stroke patients found no difference in the proportion of participants with abnormal echocardiographic findings [11]. Similarly, the prevalence of cardiac abnormalities, including myocardial infarction, dilated cardiomyopathy, left ventricular hypertrophy, valvular heart disease and infective endocarditis, were not significantly different by HIV serostatus [10,11,25].

Traditional risk factors for stroke

Cardiovascular risk factors were infrequently assessed in the published literature. Among those that reported on traditional cardiovascular risk factors, they tended to be less common among PLWH than in the general population (Supplementary Table S2). For example, dyslipidemia was a risk factor in only 0 to 14% of study participants in this review, while smoking was reported in 14 to 27% [11,19]. Hypertension, which is known to be a major determinant of stroke in sub-Saharan Africa [7], was also relatively rare, aside from one small study (n=17) which documented it in all participants evaluated [25].

Stroke Outcomes

Commonly reported outcome measures included length of hospital stay and measures of neurological disability such as the modified Rankin Scale (mRS) and mean Beta Score (mBS). In-hospital mortality rates were not reported in any of the studies. In hospital

complications such as pulmonary embolism, septicemia, and deep venous thrombosis were higher in the HIV-infected patients compared to HIV uninfected stroke patients [11,19]. For example, rates of pulmonary embolism were higher in PLWH with stroke compared with HIV uninfected stroke patients in one study (6.2% vs 2.8%, P=0.03) [19]. In another study, deep venous thrombosis occurred more frequently in PLWH with stroke compared to HIV uninfected (13% vs 4% P=0.020). This is consistent with the observed pattern of abnormal coagulation in PLWH [11]. The mean hospital length of stay in one study was 31 days [19], which contrasts to that reported after stroke in the general stroke population in SSA, in whom median length of stay is typically less than 10 days [37,38].

At the time of hospital presentation, the level of disability was substantially higher among PLWH compared to the HIV-uninfected individuals. For example, in one study from Benin, the proportion of patients with an NIHSS >13 was higher in PLWH as compared to the HIV-uninfected stroke patients (71.7% vs 32.6%, P=0.02) [19]. There is evidence, however, that disability after stroke can improve among PLWH. For example, the mean Beta Score (mBS) among PLWH in a study from South Africa increased from 56 on admission to 96 at discharge with occupational and speech therapy, suggesting a substantial improvement in daily functional activity [39]. A second study also demonstrated a marked decrease in stroke severity from admission to 30 days in a cohort of PLWH with stroke compared with HIV-uninfected stroke patients [19]. Moreover, differences in long term disability appear to be less stark between PLWH and HIV-uninfected groups. A Malawian study observing patients for one year after stroke found that the proportion of PLWH with a significant functional disability (mRS > 2) was 65% at week 6, 50% at 6 months and 32% (8/25) at 1 year post stroke. These rates were similar to those in the HIV-uninfected group [21].

Only two studies reported death rates after stroke. In one study of 113 PLWH and 319 HIV uninfected stroke patients in Benin, 30-day mortality rates were significantly higher among PLWH than HIV-uninfected subjects, although in a second study in Malawi (50 PLWH and 84 HIV uninfected), mortality rates at 6 months and at 1-year were largely similar [19,21] (Fig 3).

Discussion

We present results of a systematic review of all published studies describing clinical characteristics and outcomes of stroke among PLWH in sub-Saharan Africa. We found that: a) stroke in PLWH occurs at relatively young ages; b) patients commonly present with stroke as the initial manifestation of HIV infection; c) HIV-infected patients with stroke in SSA tend to have advanced, untreated HIV disease with high rates of concurrent opportunistic infection and low CD4 counts; d) Up to 96% of stroke in PLWH in SSA is due to the ischemic subtype, which is significantly higher than the 50–70% in the general population in the region; f) compared to HIV-uninfected patients, PLWH tended to have a longer hospital stay (up to 30 days in one study) and higher 30 day mortality rate. Beyond 30 days however, one study found similar rates of mortality and morbidity between PLWH and HIV-uninfected stroke survivors suggesting that mortality and morbidity rates tend to even out with time (Figure 3) [19,21].

Our finding that HIV-infected stroke patients present at a young age in Africa is consistent with data from other parts of the world [6,40]. A matched cohort study from the United States reported a median age of 42 years among PLWH with stroke [6], and a recent meta-analysis on the incidence and clinical features of stroke in PLWH patients revealed a median age of 46 years (IQR 46–50) [40]. PLWH and stroke putatively present at a younger age due to multiple factors, including relationships between HIV and CNS opportunistic infections [41], chronic inflammation with accelerated atherosclerosis, [42] abnormal coagulation [10,33] and abnormal vessel pathology due to HIV infection [35], which all increase stroke risk.

The realization that stroke risk in this population is associated with advanced disease, opportunistic infections, initial presentations of disease, and absence of ART use, is both a reminder of the extensive impact of HIV infection on health in the region and a cause for optimism. Because late presentation to care with HIV remains common in the region [42], clinicians should consider HIV infection in the differential of stroke, and consider both HIV testing and treatment in the management of such patients. Future studies should also focus on identifying patients at high risk of stroke at the time of enrollment into ART programs, and consider whether preventative therapies (e.g. antiplatelet agents, anticoagulants, HMG Co-A reductase inhibitors) might have a role. Conversely, given the association between stroke risk and immunodeficiency, the expansion of ART availability might also reduce the burden of stroke in the SSA region. Indeed, recent WHO guidelines to provide treatment to all PLWH regardless of CD4 count have been adopted in South Africa, Botswana, Rwanda, Uganda, and elsewhere [43], and it will be important to measure the impact of these programs on stroke and other non-AIDS outcomes as one of many secondary benefits to treatment expansion. The role of Immune reconstitution in stroke pathogenesis also needs to be evaluated as the massive role out of ART continues.

We found that ischemic stroke was more common among PLWH than among HIV-uninfected individuals. The reason for this difference is not immediately clear, but does suggest that primary stroke prevention strategies might differ for PLWH. Such measures should include use of anticoagulants, early optimization of appropriate antiretroviral therapy (and consideration of their effects on lipids), promotion of viral suppression, detection and management of concurrent opportunistic infections, and consideration of other cardiovascular disease risk factors related to physical activity, diet, cholesterol, blood pressure and diabetes management. Whereas cardiovascular disease risk prediction among PLWH remains an active area of study [44], such risk prediction tools will need to be re-evaluated in the SSA setting to ensure region-specific validity.

The high rates of in-hospital complications, longer length of hospital stay and 30-day mortality rates among HIV infected stroke patients may be related to advanced immunosuppression and co-infections commonly reported among PLWH with stroke. However, this review also demonstrated that PLWH who survive stroke commonly have significant clinical improvement in terms of long term disability (Figure 3). The phenomenon of converging outcomes irrespective of HIV serostatus among survivors of stroke might be attributable to the younger age at presentation for people with HIV, who should be afforded an improved neuroplasticity and better post stroke recovery rates compared to their older HIV uninfected counterparts [45,46]. Key interventions that may

promote neurologic recovery included occupational and speech therapy involvement and management of concurrent infections [39]. The marked improvement in disability rates between admission and discharge provides strong rationale for aggressive, multidisciplinary rehabilitative care for PLWH, who benefit from their young age and often demonstrate general clinical response with HIV viral suppression [47].

Our review was limited by the overall low abundance of data on stroke among PLWH in sub-Saharan Africa, which required us to extrapolate information from studies of small sample size and limited (or no) longitudinal observation. Only one case control study had a community component, limiting our findings to considerations of stroke among patients who present to the hospital. Also, most of the studies were conducted in the era prior to widespread ART availability, and thus the impact of chronic suppressed HIV infection was not assessed here.

In summary, stroke among HIV-infected individuals in SSA appears to disproportionately affect young individuals with advanced stages of HIV infection and naïve to ART. As such, a high suspicion for HIV-infection among stroke patients, particularly in younger age groups should be maintained. Interventions to promote earlier diagnosis of HIV and linkage to ART might help prevent stroke incidence in this population. Among those who suffer stroke, although early disability and mortality appear to be higher among PLWH, long term outcomes among survivors are reasonable, and aggressive rehabilitative management might help reduce the burden of long term disability after stroke in this population. Population based studies with longer observation periods, as well as translational studies to characterize risks of stroke in stably controlled HIV disease, are needed to help better describe causal relationships between HIV infection and stroke risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Bor J, Herbst A, Newell M-L, Barnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. Science (80-). 2013;2 22(339):6122.
2. May MT, Gompels M, Delpech V, et al. Impact on life expectancy of HIV-1 positive individuals of CD4 R cell count and viral load response to antiretroviral therapy. AIDS. 2014;28(8):1193–1202. [PubMed: 24556869]
3. Nsanzimana S, Remera E, Kanters S, et al. Life expectancy among HIV-positive patients in Rwanda: A retrospective observational cohort study. Lancet Glob Heal. 2015;3(3):e169–e177.
4. Muronya W, Sanga E, Talama G. Cardiovascular risk factors in adult Malawians on long-term antiretroviral therapy. Trans R Soc Trop Med Hyg. 2011;105(11):644–649. [PubMed: 21924753]

5. Rasmussen LD, Engsig FN, Christensen H, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS. 2011;25(13):1637–1646. [PubMed: 21646903]
6. Chow FC, Regan S, Feske S, et al. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. J Acquir Immune Defic Syndr. 2012;60(4): 351–358. [PubMed: 22580566]
7. Benjamin LA, Corbett EL, Connor MD, et al. HIV, antiretroviral treatment, hypertension, and stroke in Malawian adults: A case-control study. Neurology. 2016;86(4):324–333. [PubMed: 26683649]
8. Cole JW, Pinto AN, Hebel JR, et al. Acquired Immunodeficiency Syndrome and the Risk of Stroke. Stroke. 2004;35(1):51–56. [PubMed: 14684782]
9. Walker RW, Jusabani A, Aris E, et al. Stroke risk factors in an incident population in urban and rural Tanzania: A prospective, community-based, case-control study. Lancet Glob Heal. 2013;1(5):e282–e288.
10. Mochan A, Modi M, Modi G. Stroke in black South African HIV-positive patients: a prospective analysis. Stroke. 2003;34(1):10–15. [PubMed: 12511743]
11. Tipping B, de Villiers L, Wainwright H, et al. Stroke in patients with human immunodeficiency virus infection. J Neurol Neurosurg Psychiatry. 2007;78(12):1320–1324. [PubMed: 17470469]
12. Feigin VL. Stroke in developing countries: can the epidemic be stopped and outcomes improved? Lancet Neurol. 2007;6(2):94–97. [PubMed: 17239789]
13. Fettig J, Swaminathan M, Murrill CS, et al. Global epidemiology of HIV. Infect Dis Clin North Am. 2014;28(3):323–337. [PubMed: 25151559]
14. Adeloye D An estimate of the incidence and prevalence of stroke in Africa: A systematic review and meta-analysis. PLoS One. 2014;9(6).
15. Esse K, Fossati-Bellani M, Traylor A, et al. Epidemic of illicit drug use, mechanisms of action/addiction and stroke as a health hazard. Brain Behav. 2011;1(1):44–54. [PubMed: 22398980]
16. Durai PJ, Padma V, Vijaya P, et al. Stroke and thrombolysis in developing countries. Int J Stroke. 2007;2;2(1):17–26. [PubMed: 18705983]
17. Sagui E, M'Baye PS, Dubecq C, et al. Ischemic and hemorrhagic strokes in Dakar, Senegal: A hospital-based study. Stroke. 2005;36(9):1844–7. [PubMed: 16081856]
18. Walker RW, Rolfe M, Kelly PJ, et al. Mortality and recovery after stroke in The Gambia. Stroke. 2003;34(7):1604–1609. [PubMed: 12817107]
19. Gnonlonfoun D, Adjien KC, Adoukonou TA, et al. Human Immunodeficiency Virus Infection(HIV), Stroke Severity and Mortality Predictive indicator in centre National Hospitalier Et Universitaire-Hubert Koutoukou Maga(CNHU-HKM) Cotonou, Benin. African J Neurol Sci. 2013;32(2):14–21.
20. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
21. Heikinheimo T, Chimbayo D, Kumwenda JJ, et al. Stroke outcomes in Malawi, a country with high prevalence of HIV: A prospective follow-up study. PLoS One. 2012;7(3):3–8.
22. Jowi JO, Mativo PM, Musoke SS. Clinical and laboratory characteristics of hospitalised patients with neurological manifestations of HIV/aids at the Nairobi Hospital. East Afr Med J. 2007;84(2): 67–76. [PubMed: 17598667]
23. Balarabe SA, Watila MM. Immune Dysfunction in HIV infected stroke patients: Role of low CD 4 counts. Niger J Basic Appl Sci. 2015;23(1):51–54.
24. Hoffmann M, Berger JR, Nath A, et al. Cerebrovascular disease in young, HIV-infected, black Africans in the KwaZulu Natal province of South Africa. J Neurovirol. 2000;6(3):229–236. [PubMed: 10878712]
25. Longo-Mbenza B, Longokolo Mashi M, Lelo Tshikwela M, et al. Relationship between Younger Age, Autoimmunity, Cardiometabolic Risk, Oxidative Stress, HAART, and Ischemic Stroke in Africans with HIV/AIDS. ISRN Cardiol. 2011;2011:897908. [PubMed: 22347662]
26. Taylor A, Lefeuvre D, Levy A, et al. Arterial dissection and subarachnoid haemorrhage in human immunodeficiency virus-infected patients. A report of three cases. Interv Neuroradiol. 2004;10(2): 137–143. [PubMed: 20587225]

27. Lefeuvre D, Liebenberg L, Taylor A. Intracranial Arterial Dissection Related to HIV Infection. A Case Report with Histology. Interv Neuroradiol. 2005;11(4):387–391. [PubMed: 20584453]
28. Kumwenda JJ, Mateyu G, Kampondeni S, et al. Differential diagnosis of stroke in a setting of high HIV prevalence in blantyre, Malawi. Stroke. 2005;36(5):960–964. [PubMed: 15802634]
29. Cowppli-bony P, Oka DND. Cas clinique Tuberculose et accident vasculaire cérébral: un cas et revue de la littérature. Rev Neurol (Paris). 2005;15:201–204.
30. Benjamin LA, Bryer A, Emsley HCA, et al. HIV infection and stroke: Current perspectives and future directions. Lancet Neurol. 2012;11(10):878–890. [PubMed: 22995692]
31. Patel V, Sacoor Z, Francis P, et al. Ischemic stroke in young HIV-positive patients in Kwazulu-Natal, South Africa. Neurology. 2005;65(5):759–761. [PubMed: 16157915]
32. Walker RW, Jusabani A, Aris E, et al. Pilot study of antibodies against varicella zoster virus and human immunodeficiency virus in relation to the risk of developing stroke, nested within a rural cohort in Uganda. J Neurovirol. 2005;27(3):303.
33. Allie S, Stanley A, Bryer A, et al. High levels of von willebrand factor and low levels of its cleaving protease, ADAMTS13, are associated with stroke in young HIV-infected patients. Int J Stroke. 2015;10(8):1294–1296. [PubMed: 26121272]
34. Hoffmann M Stroke in the young in South Africa - An analysis of 320 patients. South African Med J. 2000;90(12):1226–1234.
35. Tipping B, De Villiers L, Candy S, et al. Stroke Caused by Human Immunodeficiency Virus–Associated Intracranial Large-Vessel Aneurysmal Vasculopathy. Arch Neurol. 2006;63:1640–1642. [PubMed: 17101835]
36. Corr PD. Imaging of cerebrovascular and cardiovascular disease in AIDS patients. Am J Roentgenol. 2006;187(1):236–241. [PubMed: 16794182]
37. Nakibuuka J, Sajatovic M, Nankabirwa J, et al. Early mortality and functional outcome after acute stroke in Uganda: prospective study with 30 day follow-up. Springerplus. 2015;4:450. [PubMed: 26322256]
38. Garbusinski JM, Van Der Sande MAB, Bartholome EJ, et al. Stroke presentation and outcome in developing countries: A prospective study in The Gambia. Stroke. 2005;36(7):1388–1393. [PubMed: 15947255]
39. Van Rensburg JJ. The differences in functional recovery between patients with stroke who are HIV positive and those who are HIV negative. Available from; http://hdl.handle.net/10539/17451. 2014.
40. D'Ascenzo F, Quadri G, Cerrato E, et al. A meta-analysis investigating incidence and features of stroke in HIV-infected patients in the highly active antiretroviral therapy era. J Cardiovasc Med. 2015;16(12):839–843.
41. Spudich S, Gonzalez-Scarano F. HIV-1-related central nervous system disease: current issues in pathogenesis, diagnosis, and treatment. Cold Spring Harb Perspect Med. 2012;6;2(6):a007120. [PubMed: 22675662]
42. Siedner MJ, Kim JH, Nakku RS, et al. Persistent immune activation and carotid atherosclerosis in HIV-infected ugandans receiving antiretroviral therapy. J Infect Dis. 2016;213(3):370–378. [PubMed: 26347573]
43. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection Recommendations for a public health approach - Second edition. (ISBN: 978 92 4 154968 4):Number of pages: 480.
44. Nery MW, Martelli CMT, Aparecida Silveira E, et al. Cardiovascular risk assessment: A comparison of the Framingham, PROCAM, and DAD equations in HIV-infected persons. Sci World J. 2013;10 21:969281.
45. Johansson BB. Brain Plasticity and Stroke Rehabilitation. Stroke. 2000;31:223–230. [PubMed: 10625741]
46. Cramer SC, Sur M, Dobkin BH, et al. Harnessing neuroplasticity for clinical applications. Brain. 2011;134(6):1591–1609. [PubMed: 21482550]
47. Gutierrez F, Padilla S, Masiá M, et al. Clinical outcome of HIV-infected patients with sustained virologic response to antiretroviral therapy: Long-term follow-up of a multicenter cohort. PLoS One. 2006;1(1). doi:10.1371/journal.pone.0000089.

48. Watila M, Nyandaiti Y, Balarabe S, et al. Risk factor profile among black stroke patients in Northeastern Nigeria. J Neurosci Behav Heal. 2012;4(5):50–58.

49. Kleindorfer DO, Khoury J, Moomaw CJ, et al. Stroke incidence is decreasing in whites but not in blacks: A population-based estimate of temporal trends in stroke incidence from the greater cincinnati/northern kentucky stroke study. Stroke. 2010;41(7):1326–1331. [PubMed: 20489177]

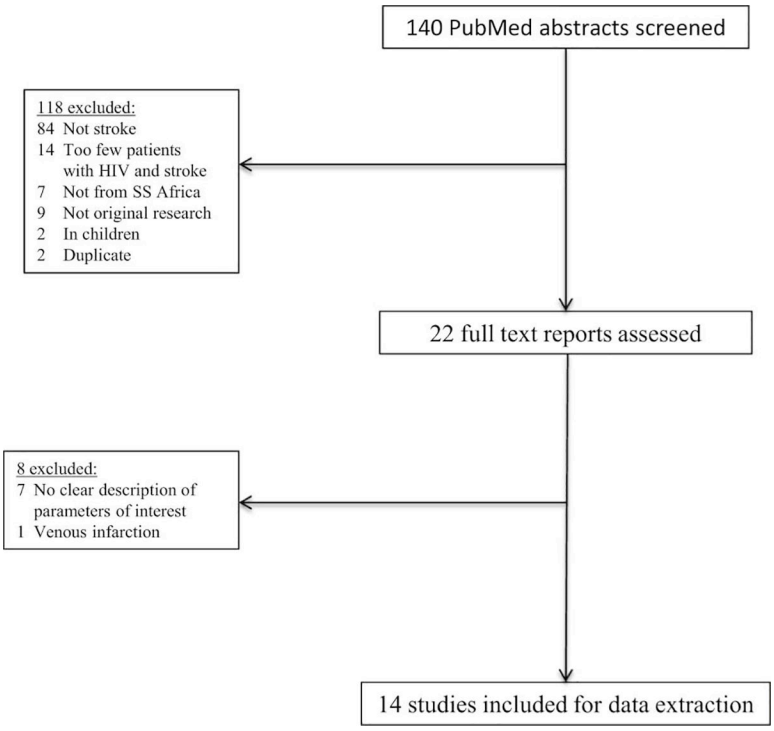

Figure 1.
Details of search and study inclusion from PubMed alone.

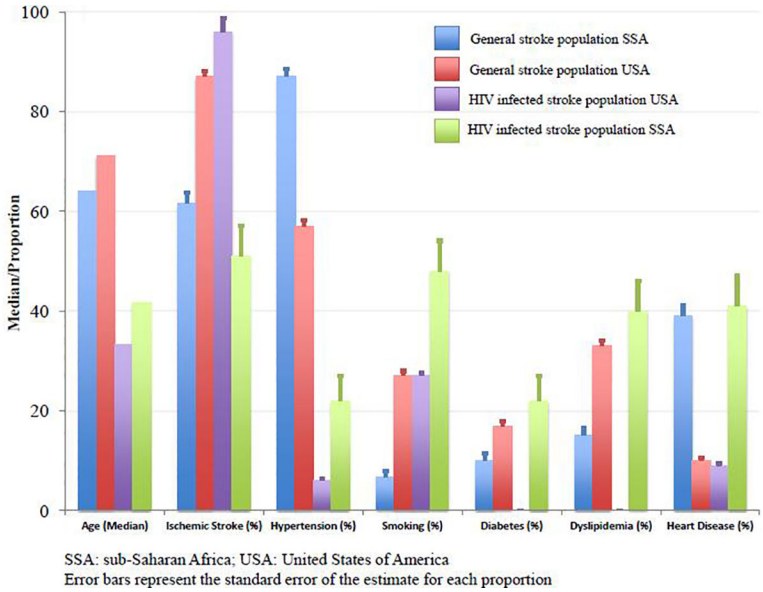

Figure 2: A comparison of the prevalence of stroke risk factors in different populations with stroke.

The figure below shows a comparison of four different studies that have been conducted in different population groups. It gives a snapshot of the contrast in median age and prevalence of certain traditional cardiovascular risk factors as reported from different settings. We have reported findings from the following groups: (a) general stroke patients in Nigeria, [48](b) general black stroke population in USA [49] (c) HIV infected stroke population in USA [6](d) HIV infected stroke population in South Africa [11].

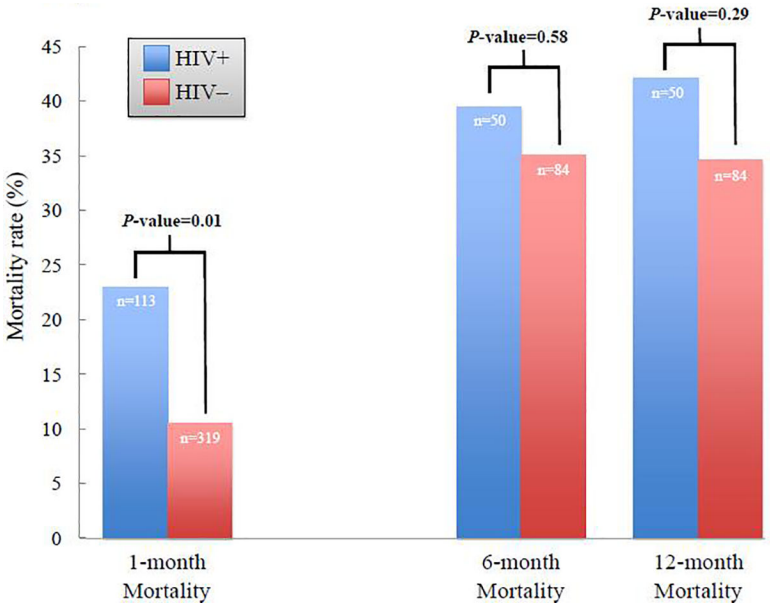

Figure 3: Stroke mortality rates in PLWH versus HIV-uninfected individuals from two studies from sub-Saharan Africa [19,21].

This figure is a summary of findings from two cohort studies, which compared mortality outcomes in PLWH with stroke versus HIV uninfected stroke patients. The first study found a significant difference in 30-day mortality rates between PLWH and HIV uninfected patients (23% vs. 10.5%, p = 0.007) respectively. The second study had a much longer follow up period and found no difference in mortality rates at 6 month and 1 year between PLWH and HIV uninfected.

Table 1:

Characteristics of all studies included.

A majority were case-control and cross-sectional studies. Three of the studies were case reports. All studies were hospital based and conducted in East, West and South Africa.

Year	First Author	Country	Ref	Sample size, n (HIV+)	Study design
2000	Hoffmann M.	South Africa	[25]	22	Case Control
2003	Mochan A.	South Africa	[10]	35	Cross Sectional
2004	Taylor A.	South Africa	[48]	3	Case Series
2005	Lefeuvre D.	South Africa	[36]	1	Case Report
2005	Patel VB.	South Africa	[30]	56	Case Control
2005	Cowppli-bony P.	Côte-d'Ivoire	[49]	1	Case Report
2006	Corr PD.	South Africa	[35]	1	Case Report
2007	Jowi JO.	Kenya	[23]	19	Cross Sectional
2007	Tipping B.	South Africa	[11]	67	Cohort
2011	Longo-Mbenza B.	Congo	[26]	17	Cross Sectional
2012	Heikinheimo T.	Malawi	[22]	50	Cohort
2013	Gnonlonfoun D.	Benin	[19]	113	Cohort
2014	Rensburg J.	South Africa	[39]	21	Cohort
2015	Allie S.	South Africa	[32]	20	Case Control
2015	Balarabe S.A.	Nigeria	[24]	20	Case Control
2016	Benjamin L.	Malawi	[7]	31	Case Control

Table 2.

Clinical and radiological characteristics of patients with stroke and HIV-infection in sub-Saharan Africa.

PLWH had a median age ranging from 32 – 43 years at the time of presentation, with low CD4 counts (median CD4 range of 108 – 225 cells/μl). Most patients were ART naïve and were presenting without an unknown HIV status. Ischemic stroke accounted for up to 96% of strokes, and most occurred in the anterior circulation territory. In the studies that graded stroke severity using the NIHSS scale, 63.1% and 71% of PLWH had a score of > 12 and >13 respectively.

Year	Country	Ref	Mean Age (years)	Sex (M:F ratio)	Mean CD4 (cells/mm^3)	CD4 < 200 or <250$^+$ (cells/mm^3) (%)	On ART (%)	Unknown HIV status at stroke diagnosis (%)	Elevated NIHSS (%)	Ischemic Stroke (%)	Anterior Circulation (ischemic, %)	Posterior Circulation (ischemic, %)
2000	South Africa	24	NR	1.4:1.0	NR	NR	NR	NR	NR	100.0	81.0	10.0
2003	South Africa	10	32.1	1.5:1.0	NR	40.0	NR	57.0	NR	94.0	94.0	6.0
2007	Kenya	22	39.0	1.4:1.0	120.0	51.3	NR	NR	NR	96.0	NR	NR
2007	South Africa	11	33.4	0.5:1.0	NR	46.0	11.9	42.0	NR	96.0	89.0	13.0
2011	Congo	25	NR	NR	107.6	NR	100.0	66.7	NR	94.0	82.4	17.6
2012	Malawi	21	39.8	0.9:1.0	NR	62.8$^+$	22.0	NR	63.1 (>12)	80.0	94.0	6.0
2013	Benin	19	43.1	1.0:1.0	119.0	NR	0.0	100.0	71.7 (>13)	67.3	NR	NR
2015	Nigeria	23	36.4	1.4:1.0	224.9	69.0	NR	NR	NR	NR	NR	NR

NR: not reported; NIHSS: National Institutes of Health Stroke Scale; ART: Antiretroviral Therapy