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Types of stroke among people living with HIV in the United States

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Abstract

Background: Most studies of stroke in people living with HIV (PLWH) do not use verified stroke diagnoses, are small, and/or do not differentiate stroke types and subtypes.

Setting: CNICS, a U.S. multisite clinical cohort of PLWH in care.

Methods: We implemented a centralized adjudication stroke protocol to identify stroke type, subtype and precipitating conditions identified as direct causes including infection and illicit drug use in a large diverse HIV cohort.

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Results: Among 26,514 PLWH, there were 401 strokes, 75% of which were ischemic. A precipitating factor such as sepsis or same-day cocaine use were identified in 40% of ischemic strokes. Those with precipitating factors were younger, had more severe HIV disease, and fewer traditional stroke risk factors such as diabetes and hypertension. Ischemic stroke subtypes included cardioembolic (20%), large vessel atherosclerosis (13%), and small vessel (24%) ischemic strokes. Individuals with small vessel strokes were older, were more likely to have a higher current CD4 cell count than those with cardioembolic strokes and had the highest mean blood pressure of the ischemic stroke subtypes.

Conclusion: Ischemic stroke, particularly small vessel and cardioembolic subtypes, were the most common strokes among PLWH. Traditional and HIV-related risk factors differed by stroke type/subtype. Precipitating factors including infections and drug use were common. These results suggest that there may be different biological phenomena occurring among PLWH and that understanding HIV-related and traditional risk factors and in particular precipitating factors for each type/subtype may be key to understanding, and therefore preventing, strokes among PLWH.

Keywords

HIV; stroke; ischemic stroke; hemorrhagic stroke; stroke subtypes

INTRODUCTION

Many unaddressed questions exist regarding strokes among people living with HIV (PLWH). PLWH have higher stroke rates than those without HIV, due at least in part to ischemic strokes[1–12], although the extent of these differences particularly which ischemic subtypes predominate is unknown. In the current treatment era, antiretroviral therapy (ART) has reduced HIV-related morbidity and mortality[13–16] and may be reducing stroke rates[10]; however, it is not clear if this applies to all stroke types and subtypes. Understanding stroke subtypes among PLWH may be important for future investigations into the pathogenesis of elevated stroke risk, including developing novel interventions to modify stroke risk[17].

Prior studies of stroke in PLWH have often used strokes that are neither verified nor adjudicated, but instead are from billing or administrative diagnosis data (e.g. International Classification of Diseases codes)[2,7–12,18–23], or based on site event forms rather than primary data review for validation[24,25]. Prior studies were often small, single center, and/or with small numbers of strokes[26–31], were conducted prior to or early in the ART treatment era[1,3,8,18,32], and did not differentiate stroke types and subtypes[2,5,11,12,18,20,22–24,33–35]. This has left unanswered questions regarding stroke and stroke types among PLWH.

The study of stroke requires sensitive stroke identification (case ascertainment), accurate confirmation of events (expert adjudication), and clearly defined clinical endpoints including stroke types. We developed and implemented a stroke adjudication protocol in Centers for AIDS Research Network of Integrated Clinical Systems (CNICS). We conducted this study to characterize stroke types and subtypes in a large diverse cohort of PLWH to better understand strokes and identify their precipitating factors, such as infections and illicit drug use.

METHODS

Study cohort

The CNICS cohort includes PLWH receiving care at 8 sites across the US[36]. The CNICS data repository integrates comprehensive clinical data from all outpatient and inpatient encounters[36]. Individuals who had a potential incident stroke event from 5 sites (Johns Hopkins University; University of Alabama at Birmingham; University of California San Diego; University of North Carolina at Chapel Hill; and University of Washington) were included in these analyses. Sites received human subjects approval for CNICS.

CNICS Data

The CNICS data repository systematically captures diagnoses; laboratory test results; medications; and procedure codes such as cerebral angiography for PLWH from the electronic health record (EHR) and other institutional data systems[36].

Potential stroke events

Potential strokes are identified centrally (ascertained) from the CNICS data repository using multiple criteria to enhance sensitivity (Figure 1). Ascertainment dates vary somewhat by site but are ~2009–2018. For every potential stroke identified, sites assemble a packet including a standardized set of clinical information for central review including elements such as provider notes and imaging and procedure results. Completed packets are uploaded to the CNICS web-based stroke adjudication platform for review. Packets are centrally reviewed by two neurologists (3 if reviews differ) using a secure web-based application designed for CNICS stroke adjudication, based on a similar application established for CNICS myocardial infarction adjudication[37,38]. The platform supports efficient management of packets and adjudication while allowing reviewers to work remotely, to classify the event, and to enter additional standardized data. The CNICS stroke protocol was based on and expanded from the Multi-Ethnic Study of Atherosclerosis well-established stroke protocol[39,40]. Strokes were categorized by stroke type (ischemic vs. intraparenchymal hemorrhagic vs. subarachnoid hemorrhagic), and by ischemic stroke subtype (small vessel, cardioembolic, large vessel atherosclerosis sometimes referred to as atheroembolic, other specified subtype, and unknown subtype including those with incomplete work-up or without reviewer consensus on subtype) based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[41]. Reviewers identified precipitating factors including infection (such as sepsis, endocarditis, and bacterial meningitis) or illicit drug use (such as same-day cocaine or methamphetamine use prior to developing stroke symptoms) identified as a direct cause and identified if the patient died as part of the reviewed event (within 31 days).

Statistical analyses

We excluded individuals whose strokes occurred prior to HIV diagnosis or enrollment in care. We included all strokes (definite, probable, and possible) but not transient ischemic attacks (TIAs) which made up ~2% of all potential events reviewed. We only included the first stroke per PLWH. We used Chi-squared tests for categorical variables and t-tests for continuous variables to assess differences in demographic and clinical characteristics

by stroke type (ischemic vs. hemorrhagic); ischemic stroke among those with and without precipitating infections or illicit drug use identified as a direct cause of the stroke; and ischemic stroke subtype. For stroke type, we combined intraparenchymal and subarachnoid hemorrhagic strokes together as hemorrhagic strokes. Traditional risk factors examined included age, sex, self-reported race/ethnicity, smoking, treated hypertension (defined as hypertension resulting in pharmacologic treatment), systolic and diastolic blood pressure, kidney function (estimated glomerular filtration rate; eGFR)[42], and body mass index (BMI) based on closest values prior to the stroke. Dyslipidemia was defined as having been prescribed lipid-lowering medications, specifically HMG Co-A reductase inhibitors (statins); we also examined lipid values prior to the stroke, including total cholesterol, high density lipoprotein cholesterol (HDL), non-high density lipoprotein cholesterol (non-HDL), low density lipoprotein cholesterol (LDL), and triglyceride values. Diabetes was based on any of the following criteria prior to or within 30 days after the stroke: a) hemoglobin A1c ≥6.5, OR b) use of a diabetes-specific medication such as insulin, OR c) use of a diabetes-related medication frequently but not exclusively used to treat diabetes (e.g. biguanides) in the setting of also having a diabetes diagnosis[43]. We examined 10-year atherosclerotic cardiovascular disease (CVD) risk using the ASCVD Pooled Cohort Equation prior to the stroke[44]. HIV-specific risk factors examined were mode of HIV transmission, CD4 (nadir or lowest, and closest prior to stroke), and HIV viral load (closest prior to stroke). We examined ART use at the time of the stroke and hepatitis B (HBV) and C (HCV) viral status based on laboratory results prior to or up to 365 days after stroke.

Results

Among 26,514 PLWH evaluated, 1045 (3.9%) met ascertainment criteria for a potential stroke at least once. Among these, 401 (38% or 1.5% of the total sample) events were adjudicated as a first stroke with a case fatality rate of 8%. Among those with an adjudicated stroke, 73% were men, the median age was 48 (interquartile range [IQR] 42–56), and the current median CD4 cell count was 290 cells/mm^3 (IQR 106–561); current CD4 count was drawn a median of 56 days before the stroke (IQR 24–148 days).

Among 401 adjudicated strokes, 302 (75%) were ischemic (Figure 2), 52 (13%) were hemorrhagic (31 intraparenchymal, 20 subarachnoid, and 1 other), and 47 (12%) the type was unidentified. Demographic and clinical characteristics by stroke type are described in Table 1. Compared to those who had a hemorrhagic stroke, those who had an ischemic stroke were significantly more likely to be Black (61% vs. 50%), on ART (71% vs. 52%), and have an undetectable viral load (59% vs. 41%). Treated hypertension, a traditional stroke risk factor, was present in 38% of those with ischemic stroke vs. 25% with hemorrhagic stroke; lipid and blood pressure values from prior to the stroke were not significantly different.

Among the 302 ischemic strokes, 40% occurred in the setting of a precipitating factor. Specifically, 16% occurred in the setting of infection such as sepsis and 15% in the setting of same-day illicit drug use such as cocaine/crack and methamphetamine (Table 2); another 6% occurred in the setting of both infection AND illicit drug use. Individuals whose ischemic stroke occurred in the setting of precipitating infection or drug use were younger, more

likely to have a CD4 nadir and recent CD4<200 cells/mm^3, and more likely to have a detectable viral load compared to those whose ischemic stroke occurred in the setting of no precipitating factor (Table 2). Traditional stroke risk factors were more common among PLWH whose ischemic stroke was not associated with precipitating factors. In particular, those without precipitating factors were more likely to have diabetes (24% vs. 9%) and a higher mean SBP (135 vs. 125 mmHg) despite being more likely to be receiving treatment for hypertension (45% vs. 29%). Those who had an ischemic stroke without precipitating factors had higher total cholesterol levels (mean 184 vs. 161 mg/dL) and LDL levels (104 vs. 93 mg/dL) despite being more likely to be on statin therapy (33% vs. 14%). They also had a small but significantly higher BMI and poorer kidney function than those with precipitating factors, possibly due in part to age differences. ASCVD risk score among those who had an ischemic stroke without a precipitating factor was significantly higher than those who had precipitating factor (mean 17 vs. 11) (Table 2).

Ischemic stroke subtypes included cardioembolic (20%), large vessel atherosclerosis (13%), small vessel (24%), other (16%), and unknown (24%: 39% of which were due to incomplete work-up). Individuals with small vessel strokes were the oldest (median 53 years of age), were more likely to have a higher current CD4 cell count than those with cardioembolic strokes, and had the highest mean SBP (140mmHg vs. 121–133mmHg) and DBP (85mmHg vs. 76–79mmHg) of the stroke subtypes (Table 3). BMI varied significantly by subtype, with higher mean values among those with small vessel then cardioembolic subtypes. PLWH with large vessel atherosclerosis and small vessel subtypes had greater CVD risk than those with cardioembolic stroke subtypes as measured by ASCVD score. PLWH with cardioembolic ischemic stroke subtypes were more likely to have identified precipitating factors than those with large vessel atherosclerosis or small vessel subtypes (50 vs. 33 or 18% respectively). These differences were significantly higher for precipitating infections for cardioembolic vs. both large vessel atherosclerosis and small vessel subtypes and for precipitating drug use for small vessel (Table 3).

DISCUSSION

We examined strokes including stroke types, subtypes, and precipitating factors among PLWH in care at multiple sites across the U.S. resulting in one of the largest, most diverse evaluations to date. Ischemic strokes were more frequent than hemorrhagic strokes, with small vessel and cardioembolic most common among the identified ischemic subtypes. PLWH suffering ischemic vs. hemorrhagic strokes had different demographic and clinical characteristics, including current ART use. Precipitating factors such as illicit drug use and infections were common, occurring in 40% of ischemic strokes. Those with precipitating factors were younger, had more severe HIV disease as measured by CD4 counts, and fewer traditional stroke risk factors. These differences highlight that there may be different biological phenomena occurring among PLWH with different stroke types and subtypes, and particularly among those with precipitating factors.

Stroke types

Ischemic strokes and intracerebral hemorrhages have distinct mechanisms and risk factors, therefore the impact of HIV on these endpoints may not be the same[45]. Despite these differences, studies often use a composite stroke endpoint or stroke combined with other CVD outcomes and/or death[33,46–51]. We found that most strokes were ischemic rather than hemorrhagic, similar to the proportions observed in the general population[52,53]. The preponderance of ischemic strokes in PLWH has been seen previously[9,26], although data from large multi-site cohorts with validated endpoints rather than diagnosis codes are limited. A study of 82 strokes from an earlier era with only 37% of PLWH on ART found 77 (94%) events were ischemic and 5% were hemorrhagic[54]. A Baltimore study of 125 strokes in predominantly Black PLWH found that 69% had ischemic events[26]. In contrast, one of the larger case series to date, which identified hospitalized PLWH with cerebrovascular disease ICD-9 codes from 2002–2014 and then confirmed stroke types, found 115 ischemic vs. 7 hemorrhagic strokes[55], a much higher proportion of ischemic events than we found, although they included TIAs as ischemic strokes. The difference in percentages of ischemic vs. hemorrhage strokes across studies is likely multifactorial, including differing populations, ascertainment approaches, HIV treatment era, and in the case of some studies, the inclusion of TIAs in the ischemic stroke category.

Stroke subtypes

Understanding stroke etiology or mechanisms, including ischemic stroke characterization, is key to risk factor modification and stroke prevention[56,57]. It has therefore been proposed to move from defining stroke as a homogenous endpoint to focus on stroke subtype pathophysiology[55], as the distribution of stroke subtypes could provide insight into possible mechanisms leading to higher stroke risk among PLWH[45], as well as guidance in predicting recurrent stroke risk and prognosis[58]. While the TOAST criteria are not the only way to categorize ischemic strokes, they are the most commonly used classification scheme[56]. There are three identified ischemic stroke subtypes: cardioembolic due to causes such as atrial fibrillation or endocarditis; large artery atherosclerosis due to large vessel stenosis such as in the internal carotid arteries; and small vessel or lacunar strokes. Ischemic strokes can also be categorized as other specified subtype or unknown subtype.

Several studies have applied TOAST criteria to PLWH, although they were often small, single-site studies or early in the ART treatment era with a lower proportion on ART. Overall, these studies have suggested that large vessel atherosclerosis and small vessel subtypes may be more common than cardioembolic subtypes[58]. For example, a Baltimore study from 2000–2012 found 72 ischemic strokes among 105 Black PLWH who had a stroke; of these ischemic strokes, small vessel was the most commonly identified subtype (44%), but in contrast to our findings, the next most common subtype was large vessel atherosclerosis (31%)[26]. Similarly, a study from 1999–2010 found that among 31 ischemic strokes, 13 (42%) were large vessel atherosclerosis, 11 (35%) were small vessel, and 1 (3%) was cardioembolic[59]. Another study from Madrid, Spain identified 22 ischemic strokes between 1996–2008 among PLWH on ART of which 6 (24%) were large vessel atherosclerosis, 6 (24%) small vessel, and 2 (8%) cardioembolism[60]. While these results are interesting, they are based on small numbers. We found that among 302 ischemic strokes,

small vessel (24%) and cardioembolic (20%) subtypes were the most commonly identified types, followed by large vessel atherosclerosis (13%). A similar pattern was reported in a single site study in PLWH between 1996–2005 that found of 77 ischemic strokes, 19% were small vessel, 19% cardioembolic, and 13% large vessel atherosclerosis[54].

A key finding of prior work is that the proportion of events that cannot be classified as one of the 3 main TOAST subtypes, but instead are classified as unknown or cryptogenic or due to multiple etiologies, is higher in PLWH than the general population[54,61], although rates of cryptogenic stroke even in the general population have been variable, ranging from 13 to 51%[62]. We found that among ischemic strokes, 16% were subtyped as other (specified) and 28% were classified as unknown (39% of which had an incomplete workup). The higher proportion of unknown/cryptogenic ischemic strokes has raised the question of whether this is due to practice variation in the work-up of strokes vs. novel stroke mechanisms among PLWH[58].

Precipitating factors

In addition to vascular risk factors, which increase the likelihood of stroke in the general population, precipitating factors have been identified as “stroke triggers”[63]. While many stroke triggers have been considered in the general population, such as being postpartum and cervical manipulation, their absolute contribution to stroke risk remains small[64]. We focused on two categories that are prevalent among PLWH, specifically infections and drug use, and identified direct precipitating factors in 40% of ischemic strokes in PLWH, a rate higher than other populations[64]. Early studies among PLWH found that strokes often occurred in the setting of advanced AIDS and opportunistic infections, including cryptococcosis, tuberculosis, zoster vasculitis, or other infections such as endocarditis[65], but much less is known about the role of opportunistic and other infections in the current treatment era. One of the largest case series among PLWH to date found that among 115 PLWH with ischemic stroke, the most common infections were bacterial endocarditis (n=6) and varicella zoster (n=5)[55]. In our study, while infections were common precipitating conditions, the most common infections were bacterial endocarditis (n=22) and sepsis (n=14) rather than opportunistic infections.

We found that there were substantial differences in traditional stroke risk factors among those with ischemic strokes with and without precipitating factors. For example, in contrast to some general population studies, we did not find older median age among those with cardioembolic strokes vs. other stroke subtypes[66]. However, half of cardioembolic strokes were associated with precipitating factors which occurred among younger PLWH (57% of strokes among those <50 were associated with a predisposing factor vs. 22% among those ≥50). Table 2 shows the characteristics of PLWH with ischemic strokes without precipitating conditions more closely resembles what might be expected from a general population with ischemic stroke.

The high proportion of younger PLWH with ischemic stroke with precipitating factors who had poorer HIV disease status and less traditional stroke risk factors appears analogous to observations of myocardial infarctions (MIs). Specifically, almost half of all MIs in PLWH are type 2 MIs occurring in the setting of causes such as sepsis and cocaine-induced

vasospasm[38] rather than traditional atheroembolic type 1 MIs. Those with type 2 MI are younger, have more advanced HIV disease, and fewer cardiovascular risk factors compared with PLWH with type 1 MIs, raising the question of broader approaches to prevention than just targeting traditional CVD risk factors. This may also apply to PLWH with stroke particularly those with precipitating conditions.

Adjudication

We used centralized ascertainment and adjudication to identify strokes, an improvement over studies that used administrative or diagnosis data[2,7–11,18–23]. While the Cardiovascular Health Study (CHS) previously found agreement was fairly high for those with inpatient stroke diagnosis codes also having a stroke by adjudication (71 of 79 events with diagnoses, or 89.9%)[67], unfortunately they also found a substantial number that did not have a stroke diagnosis (16 of 144 adjudicated events, or 11.1%, had a stroke but did not have stroke diagnoses) and therefore would be missed without broad ascertainment approaches[67]. Prior studies demonstrated for endpoints such as myocardial infarction (MI) that central adjudication is preferable to local event adjudication with or without secondary central review of case report forms which have inherent errors. Local adjudication has been shown to miss more true events than systematic centralized approaches[68] and higher rates have been found in studies employing central adjudication compared with relying on local investigator reviews or case report forms[69–72]. Two of the more rigorous HIV stroke studies to date were based on diagnoses with confirmation of endpoints by neurology reviews of 125 strokes[26] and 53 strokes[59]. Relying solely on diagnosis data without adjudication leads to disease misclassification for cardiovascular endpoints[37,67]. Furthermore, centralized adjudication provides an opportunity not only to capture whether or not a stroke occurred but also stroke types, subtypes, and precipitating factors, all of which require adjudication by expert reviewers of primary data (here done by neurologists).

Limitations

We ascertained strokes using clinical data without also obtaining Medicare hospitalization data. While it is possible more events would be ascertained by adding this approach, the CHS study found that using Medicare data added little[67] and claims-based approaches undercapture events[73]. Additionally, we could have missed those with subtle clinical symptoms that patients and providers failed to recognize as a stroke. We did not capture strokes that resulted in death before hospitalization. We do not know if identifying predisposing factors such as sepsis influenced subtype selection by reviewers. Lastly, our population is PLWH in clinical care. While this increases the likelihood of capturing relevant events, it decreases generalizability to those not in care or with undiagnosed HIV.

Strengths

To our knowledge this is the largest study to date describing strokes in PLWH in the setting of comprehensive clinical data, with centrally adjudicated strokes based on primary data. Adjudication facilitates capturing stroke type and subtypes and potential precipitating factors which are not otherwise available. The CNICS cohort provides geographic, racial/ethnic, and clinical diversity. Furthermore, this study focused on well-defined strokes rather than composite endpoints or TIAs[55,74], which were often included in prior studies.

Future studies

The importance of understanding strokes is likely only to increase given the aging population of PLWH in places such as the U.S., and the potential compounding effects of the high HIV prevalence in low and middle-income countries where stroke burden is high[75,76]. The potential implications of COVID-19 on HIV-related stroke is another future research area. Furthermore, stroke subtypes may impact long-term outcomes; long-term outcomes after ischemic strokes differ by stroke type in the general population[77] but little is known about long-term outcomes after strokes among PLWH.

Conclusions

Large epidemiological studies with carefully adjudicated strokes and clearly defined stroke types, subtypes, and comprehensive clinical data to better understand risk factors and causes of stroke will better inform interventions designed to improve clinical management and reduce risk. Ischemic stroke, particularly small vessel and cardioembolic ischemic stroke subtypes, are the most common strokes among PLWH. This study is the first to report the high proportion of strokes among PLWH with precipitating factors (40% of ischemic strokes). Those with precipitating factors were younger, had more severe HIV disease, and fewer traditional stroke risk factors, highlighting that traditional stroke prevention approaches may work less well in PLWH. These differences suggest that there may be different biological phenomena occurring among PLWH with strokes and that understanding types, subtypes, and precipitating factors is key to understanding, and therefore preventing, strokes among PLWH.

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REFERENCES

1. Qureshi AI, Janssen RS, Karon JM, et al. Human immunodeficiency virus infection and stroke in young patients. Arch Neurol. 1997;54(9):1150–1153. [PubMed: 9311359]
2. Sico JJ, Chang CC, So-Armah K, et al. HIV status and the risk of ischemic stroke among men. Neurology. 2015;84(19):1933–1940. [PubMed: 25862803]
3. Cole JW, Pinto AN, Hebel JR, et al. Acquired immunodeficiency syndrome and the risk of stroke. Stroke. 2004;35(1):51–56. [PubMed: 14684782]
4. Chow FC, Regan S, Feske S, Meigs JB, Grinspoon SK, Triant VA. 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]
5. Mateen FJ, Post WS, Sacktor N, et al. Long-term predictive value of the Framingham Risk Score for Stroke in HIV-positive vs HIV-negative men. Neurology. 2013;81(24):2094–2102. [PubMed: 24212385]
6. Rasmussen LD, May MT, Kronborg G, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. Lancet HIV. 2015;2(7):e288–298. [PubMed: 26423253]

7. Marcus JL, Leyden WA, Chao CR, et al. HIV infection and incidence of ischemic stroke. AIDS. 2014;28(13):1911–1919. [PubMed: 24937309]
8. Durand M, Sheehy O, Baril JG, LeLorier J, Tremblay CL. Risk of spontaneous intracranial hemorrhage in HIV-infected individuals: a population-based cohort study. J Stroke Cerebrovasc Dis. 2013;22(7):e34–41. [PubMed: 22554568]
9. Yen YF, Chen M, Jen I, et al. Association of HIV and opportunistic infections with incident stroke: a nationwide population-based cohort study in Taiwan. J Acquir Immune Defic Syndr. 2016.
10. Chow FC, Regan S, Zanni MV, et al. Elevated ischemic stroke risk among women living with HIV infection. AIDS. 2018;32(1):59–67. [PubMed: 28926405]
11. Alonso A, Barnes AE, Guest JL, Shah A, Shao IY, Marconi V. HIV Infection and incidence of cardiovascular diseases: An analysis of a large healthcare database. J Am Heart Assoc. 2019;8(14):e012241. [PubMed: 31266386]
12. Rosenson RS, Hubbard D, Monda KL, et al. Excess risk for atherosclerotic cardiovascular outcomes among US adults with HIV in the current era. J Am Heart Assoc. 2020;9(1):e013744. [PubMed: 31880980]
13. Palella FJ Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;338(13):853–860. [PubMed: 9516219]
14. Murphy EL, Collier AC, Kalish LA, et al. Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. Ann Intern Med. 2001;135(1):17–26. [PubMed: 11434728]
15. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. JAMA. 1998;279(6):450–454. [PubMed: 9466638]
16. Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet. 2005;366(9483):378–384. [PubMed: 16054937]
17. Chow FC, Price RW, Hsue PY, Kim AS. Greater risk of stroke of undetermined etiology in a contemporary HIV-Infected cohort compared with uninfected individuals. J Stroke Cerebrovasc Dis. 2017;26(5):1154–1160. [PubMed: 28262563]
18. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. Clin Infect Dis. 2011;53(1):84–91. [PubMed: 21653308]
19. Ovbiagele B, Nath A. Increasing incidence of ischemic stroke in patients with HIV infection. Neurology. 2011;76(5):444–450. [PubMed: 21248273]
20. LaFleur J, Bress AP, Rosenblatt L, et al. Cardiovascular outcomes among HIV-infected veterans receiving atazanavir. AIDS. 2017;31(15):2095–2106. [PubMed: 28692532]
21. Alvaro-Meca A, Berenguer J, Diaz A, et al. Stroke in HIV-infected individuals with and without HCV coinfection in Spain in the combination antiretroviral therapy era. PLoS One. 2017;12(6):e0179493. [PubMed: 28617855]
22. 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]
23. Lin HL, Muo CH, Lin CY, Chen HJ, Chen PC. Incidence of stroke in patients with HIV infection: A population-based study in Taiwan. PloS one. 2019;14(5):e0217147. [PubMed: 31116762]
24. Ryom L, Lundgren JD, El-Sadr W, et al. Cardiovascular disease and use of contemporary protease inhibitors: the D:A:D international prospective multicohort study. Lancet HIV. 2018;5(6):e291–e300. [PubMed: 29731407]
25. Hatleberg CI, Ryom L, Kamara D, et al. Predictors of ischemic and hemorrhagic strokes among people living with HIV: the D:A:D international prospective multicohort Study. EClinicalMedicine. 2019;13:91–100. [PubMed: 31517266]
26. Thakur KT, Lyons JL, Smith BR, Shinohara RT, Mateen FJ. Stroke in HIV-infected African Americans: a retrospective cohort study. J Neurovirol. 2015.

27. Chow FC, Bacchetti P, Kim AS, Price RW, Hsue PY. Effect of CD4+ cell count and viral suppression on risk of ischemic stroke in HIV infection. AIDS. 2014;28(17):2573–2577. [PubMed: 25160935]
28. Arentzen M, Jubt F, Evers S, et al. Cerebrovascular events in HIV-infected patients: an analysis of a cohort of 3203 HIV+ patients during the times of cART. Int J Neurosci. 2015;125(8):601–611. [PubMed: 25158008]
29. Silva-Pinto A, Costa A, Serrao R, Sarmento A, Abreu P. Ischaemic stroke in HIV-infected patients: a case-control study. HIV medicine. 2016.
30. 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]
31. Ances BM, Bhatt A, Vaida F, et al. Role of metabolic syndrome components in human immunodeficiency virus-associated stroke. J Neurovirol. 2009;15(3):249–256. [PubMed: 19562611]
32. Pinto AN. AIDS and cerebrovascular disease. Stroke. 1996;27(3):538–543. [PubMed: 8610326]
33. Sabin CA, Ryom L, De Wit S, et al. Associations between immune depression and cardiovascular events in HIV infection. AIDS. 2013;27(17):2735–2748. [PubMed: 23842128]
34. Sabin CA, Ryom L, Kovari H, et al. Association between ALT level and the rate of cardio/cerebrovascular events in HIV-positive individuals: the D: A: D study. Journal of Acquired Immune Deficiency Syndromes. 2013;63(4):456–463. [PubMed: 23535291]
35. Chow FC, Wilson MR, Wu K, Ellis RJ, Bosch RJ, Linas BP. Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort. AIDS. 2018;32(9):1125–1135. [PubMed: 29746317]
36. Kitahata MM, Rodriguez B, Haubrich R, et al. Cohort profile: the Centers for AIDS Research Network of Integrated Clinical Systems. Int J Epidemiol. 2008;37(5):948–955. [PubMed: 18263650]
37. Crane HM, Heckbert SR, Drozd DR, et al. Lessons learned from the design and implementation of myocardial infarction adjudication tailored for HIV clinical cohorts. Am J Epidemiol. 2014;179(8):996–1005. [PubMed: 24618065]
38. Crane HM, Paramsothy P, Drozd DR, et al. Types of myocardial infarction among Human Immunodeficiency Virus-infected individuals in the United States. JAMA Cardiol. 2017;2(3):260–267. [PubMed: 28052152]
39. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. American Journal of Epidemiology. 2002;156(9):871–881. [PubMed: 12397006]
40. O'Neal WT, Efird JT, Nazarian S, Alonso A, Heckbert SR, Soliman EZ. Peripheral arterial disease and risk of atrial fibrillation and stroke: the Multi-Ethnic Study of Atherosclerosis. J Am Heart Assoc. 2014;3(6):e001270. [PubMed: 25404190]
41. Adams HP Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24(1):35–41. [PubMed: 7678184]
42. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–612. [PubMed: 19414839]
43. Crane HM, Kadane JB, Crane PK, Kitahata MM. Diabetes case identification methods applied to electronic medical record systems: their use in HIV-infected patients. Curr HIV Res. 2006;4(1):97–106. [PubMed: 16454715]
44. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S49–73. [PubMed: 24222018]
45. Chow FC. HIV infection, vascular disease, and stroke. Semin Neurol. 2014;34(1):35–46. [PubMed: 24715487]
46. Marcus JL, Neugebauer RS, Leyden WA, et al. Use of abacavir and risk of cardiovascular disease among HIV-infected individuals. J Acquir Immune Defic Syndr. 2015.

47. Fernandez-Montero JV, Barreiro P, de Mendoza C, Labarga P, Soriano V. Hepatitis C virus coinfection independently increases the risk of cardiovascular disease in HIV-positive patients. J Viral Hepat. 2016;23(1):47–52. [PubMed: 26390144]
48. Desai M, Joyce V, Bendavid E, et al. Risk of cardiovascular events associated with current exposure to HIV antiretroviral therapies in a US veteran population. Clin Infect Dis. 2015;61(3):445–452. [PubMed: 25908684]
49. Krsak M, Kent DM, Terrin N, Holcroft C, Skinner SC, Wanke C. Myocardial infarction, stroke, and mortality in cART-treated HIV patients on statins. AIDS Patient Care STDS. 2015;29(6):307–313. [PubMed: 25855882]
50. Esser S, Eisele L, Schwarz B, et al. Rates of cardiovascular events and deaths are associated with advanced stages of HIV-infection: results of the HIV HEART study 7, 5 year follow-up. J Int AIDS Soc. 2014;17(4 Suppl 3):19542. [PubMed: 25394050]
51. D:A:D Study Investigators. Cardio- and cerebrovascular events in HIV-infected persons. AIDS. 2004;18(13):1811–1817. [PubMed: 15316342]
52. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146–e603. [PubMed: 28122885]
53. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. Circulation. 2020;141(9):e139–e596. [PubMed: 31992061]
54. Ortiz G, Koch S, Romano JG, Forteza AM, Rabinstein AA. Mechanisms of ischemic stroke in HIV-infected patients. Neurology. 2007;68(16):1257–1261. [PubMed: 17438215]
55. Gutierrez J, Hatleberg CI, Evans H, Yin MT. Role of pre-stroke immunity in ischemic stroke mechanism among patients with HIV. AIDS Care. 2018:1–5.
56. Esenwa C, Gutierrez J. Secondary stroke prevention: challenges and solutions. Vasc Health Risk Manag. 2015;11:437–450. [PubMed: 26300647]
57. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337(8756):1521–1526. [PubMed: 1675378]
58. Nguyen I, Kim AS, Chow FC. Prevention of stroke in people living with HIV. Prog Cardiovasc Dis. 2020.
59. Vinikoor MJ, Napravnik S, Floris-Moore M, Wilson S, Huang DY, Eron JJ. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the Southeastern United States. AIDS Res Hum Retroviruses. 2013;29(7):1068–1074. [PubMed: 23565888]
60. Corral I, Quereda C, Moreno A, et al. Cerebrovascular ischemic events in HIV-1-infected patients receiving highly active antiretroviral therapy: incidence and risk factors. Cerebrovasc Dis. 2009;27(6):559–563. [PubMed: 19390181]
61. Benjamin LA, Bryer A, Lucas S, et al. Arterial ischemic stroke in HIV: Defining and classifying etiology for research studies. Neurol Neuroimmunol Neuroinflamm. 2016;3(4):e254. [PubMed: 27386505]
62. Gutierrez J, Koch S, Dong C, et al. Racial and ethnic disparities in stroke subtypes: a multiethnic sample of patients with stroke. Neurol Sci. 2014;35(4):577–582. [PubMed: 24122024]
63. Moskowitz MA, Lo EH, Iadecola C. The science of stroke: mechanisms in search of treatments. Neuron. 2010;67(2):181–198. [PubMed: 20670828]
64. Elkind MS. Why now? Moving from stroke risk factors to stroke triggers. Curr Opin Neurol. 2007;20(1):51–57. [PubMed: 17215689]
65. Engstrom JW, Lowenstein DH, Bredesen DE. Cerebral infarctions and transient neurologic deficits associated with acquired immunodeficiency syndrome. Am J Med. 1989;86(5):528–532. [PubMed: 2712060]
66. Schneider AT, Kissela B, Woo D, et al. Ischemic stroke subtypes: a population-based study of incidence rates among blacks and whites. Stroke. 2004;35(7):1552–1556. [PubMed: 15155974]
67. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol. 1995;5(4):278–285. [PubMed: 8520709]

68. Mahaffey KW, Harrington RA, Akkerhuis M, et al. Systematic adjudication of myocardial infarction end-points in an international clinical trial. Curr Control Trials Cardiovasc Med. 2001;2(4):180–186. [PubMed: 11806793]
69. Mahaffey KW, Harrington RA, Akkerhuis M, et al. Disagreements between central clinical events committee and site investigator assessments of myocardial infarction endpoints in an international clinical trial: review of the PURSUIT study. Curr Control Trials Cardiovasc Med. 2001;2(4):187–194. [PubMed: 11806794]
70. The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II. Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis-II. Lancet. 1997;349(9063):1422–1428. [PubMed: 9164315]
71. Kirwan BA, Lubsen J, de Brouwer S, et al. Diagnostic criteria and adjudication process both determine published event-rates: the ACTION trial experience. Contemp Clin Trials. 2007;28(6):720–729. [PubMed: 17509947]
72. Serebruany VL, Atar D. Viewpoint: Central adjudication of myocardial infarction in outcome-driven clinical trials - Common patterns in TRITON, RECORD, and PLATO? Thromb Haemost. 2012;108(3):412–414. [PubMed: 22836596]
73. Psaty BM, Delaney JA, Arnold AM, et al. Study of Cardiovascular Health Outcomes in the Era of Claims Data: The Cardiovascular Health Study. Circulation. 2016;133(2):156–164. [PubMed: 26538580]
74. d'Arminio A, Sabin CA, Phillips AN, et al. Cardio- and cerebrovascular events in HIV-infected persons. AIDS. 2004;18(13):1811–1817. [PubMed: 15316342]
75. Bennett DA, Krishnamurthi RV, Barker-Collo S, et al. The global burden of ischemic stroke: findings of the GBD 2010 study. Glob Heart. 2014;9(1):107–112. [PubMed: 25432120]
76. Behrouz R, Gottesman RF. The merging burden of HIV infection and stroke in the developing world. Neurology. 2016;86(4):316–317. [PubMed: 26683640]
77. Redfors P, Jood K, Holmegaard L, Rosengren A, Blomstrand C, Jern C. Stroke subtype predicts outcome in young and middle-aged stroke sufferers. Acta Neurol Scand. 2012;126(5):329–335. [PubMed: 22339042]

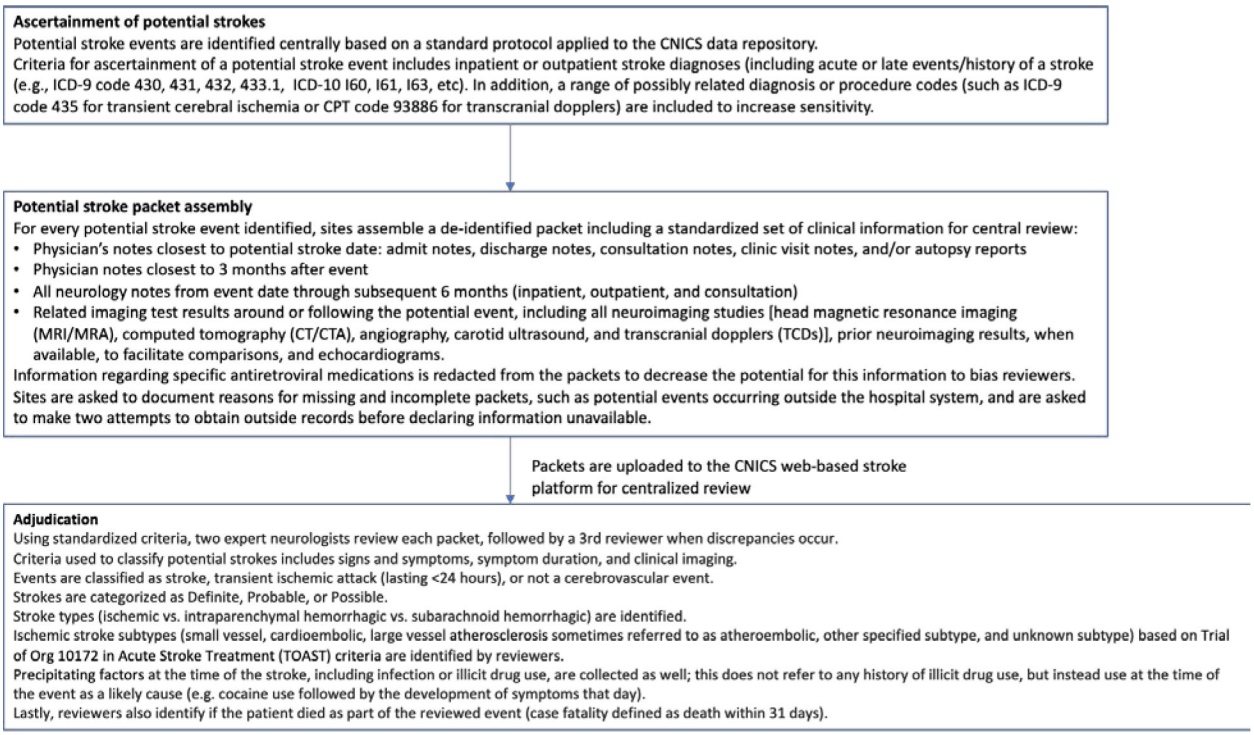

Figure 1.

Stroke ascertainment and adjudication at five sites across the United States in the CNICS cohort

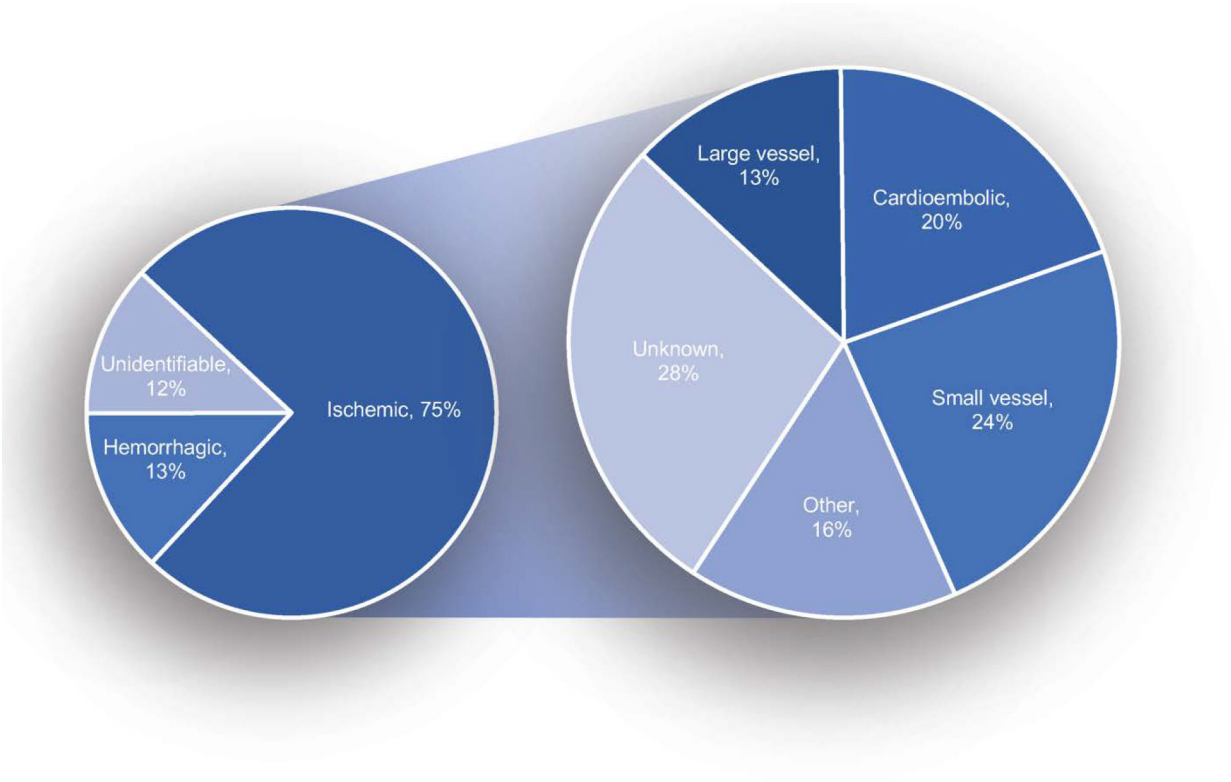

Figure 2.
Stroke types and ischemic stroke subtypes among people living with HIV at 5 sites across the United States in the CNICS cohort

Table 1.

Demographic and clinical characteristics of people living with HIV in clinical care at 5 CNICS sites across the U.S. with adjudicated stroke by stroke type

Characteristic	Total N (%)	Ischemic N (%)	Hemorrhagic N (%)	Unknown/Other N (%)	p-value^	p-value overall
N (% of total)	401	302 (75)	52 (13)	47 (12)		
Female sex	108 (27)	82 (27)	12 (23)	14 (30)	0.5	0.7
Age (years)						
<40	86 (21)	58 (19)	13 (25)	15 (32)	0.6	0.1
40–49	127 (32)	101 (33)	19 (37)	7 (15)		
50–59	132 (33)	98 (32)	15 (29)	19 (40)		
≥60	56 (14)	45 (15)	5 (10)	6 (13)		
Race/ethnicity						
White	124 (31)	93 (31)	17 (33)	14 (30)	0.009	0.03
Black	240 (60)	185 (61)	26 (50)	29 (62)		
Hispanic	30 (7)	21 (7)	5 (10)	4 (9)		
Other	7 (2)	3 (1)	4 (8)	0 (0)		
HIV transmission risk factor						
MSM	128 (32)	90 (30)	21 (40)	17 (36)	0.2	0.045
IDU	113 (28)	88 (29)	18 (35)	7 (15)		
Heterosexual	135 (34)	103 (34)	10 (19)	22 (47)		
Other	25 (6)	21 (7)	3 (6)	1 (2)		
CD4+ cell count (nadir, cells/mm^3)*						
<200	217 (67)	180 (68)	27 (71)	10 (53)	0.9	0.9
200–349	56 (17)	46 (17)	5 (13)	5 (26)		
350–499	24 (7)	19 (7)	3 (8)	2 (11)		
≥500	26 (8)	21 (8)	3 (8)	2 (11)		
CD4+ cell count (current, cells/mm^3)*						
<200	121 (37)	100 (38)	18 (47)	3 (16)	0.7	0.2
200–349	58 (18)	46 (17)	6 (16)	6 (32)		
350–499	48 (15)	38 (14)	5 (13)	5 (26)		
≥500	96 (30)	82 (31)	9 (24)	5 (26)		
Currently receiving ART	259 (65)	213 (71)	27 (52)	19 (40)	0.008	<0.001
Current undetectable viral load (<400 copies/mL)*	186 (58)	155 (59)	16 (41)	15 (75)	0.03	0.03
Hepatitis C virus	101 (25)	82 (27)	18 (35)	1 (2)	0.3	<0.001
Hepatitis B virus	26 (6)	21 (7)	4 (8)	1 (2)	0.8	0.4
Diabetes	66 (16)	55 (18)	7 (13)	4 (9)	0.4	0.2
Treated hypertension	139 (35)	116 (38)	13 (25)	10 (21)	0.06	0.02
Blood pressure (mean, SD)						
Systolic	132 (23)	131 (22)	133 (23)	142 (33)	0.6	0.2

Characteristic	Total N (%)	Ischemic N (%)	Hemorrhagic N (%)	Unknown/Other N (%)	p-value^	p-value overall
Diastolic	80 (12)	79 (12)	81 (13)	81 (12)	0.6	0.8
Statin use	95 (24)	77 (26)	7 (13)	11 (23)	0.6	0.2
Lipid levels (mean, SD)						
Total cholesterol	176 (53)	175 (50)	173 (69)	191 (60)	0.9	0.5
HDL	43 (17)	43 (17)	49 (18)	47 (16)	0.09	0.1
LDL	101 (41)	101 (39)	100 (59)	103 (36)	0.9	1.0
Triglycerides	185 (144)	185 (147)	160 (104)	227 (170)	0.2	0.3
Smoking	141 (35)	113 (37)	20 (38)	8 (17)	0.9	0.02
Kidney function (mL/min/ 1.73m^2; mean, SD)	85 (36)	88 (35)	71 (41)	74 (29)	0.02	0.007
BMI (kg/m^2; mean, SD)	26 (6)	26 (6)	24 (6)	27 (6)	0.054	0.09
ASCVD risk score (mean, SD)	15 (14)	15 (13)	12 (16)	21 (18)	0.5	0.1

* CD4 count values available from 323 PLWH; viral load values from 320 PLWH

^ Tests ischemic vs. hemorrhagic strokes

ASCVD risk score: 10-year atherosclerotic cardiovascular disease risk as measured by the ASCVD Pooled Cohort Equation; BMI: body mass index; IDU: injection drug user; MSM: men who have sex with men;

Table 2.

Demographic and clinical characteristics of people living with HIV in clinical care at 5 CNICS sites across the U.S. with ischemic stroke, by whether or not predisposing infection or drug use was identified at the time of the stroke

Characteristic	Ischemic stroke, no precipitating infection or drug use N (%)	Ischemic stroke, precipitating infection and/or drug use N (%)	p-value
N (% of ischemic strokes)	180 (60%)	122 (40%)	
Female Sex	50 (28)	32 (26)	0.8
Age (years)			
<40	19 (11)	39 (32)	<0.001
40–49	49 (27)	52 (43)	
50–59	76 (42)	22 (18)	
≥60	36 (20)	9 (7)	
Race/ethnicity			
White	64 (36)	29 (24)	0.1
Black	105 (58)	80 (66)	
Hispanic	10 (6)	11 (9)	
Other	1 (1)	2 (2)	
HIV transmission risk factor			
MSM	56 (31)	34 (28)	0.08
IDU	43 (24)	45 (37)	
Heterosexual	69 (38)	34 (28)	
Other	12 (7)	9 (7)	
CD4+ cell count (nadir, cells/mm^3)			
<200	96 (60)	84 (80)	0.007
200–349	35 (22)	11 (10)	
350–499	14 (9)	5 (5)	
≥500	16 (10)	5 (5)	
CD4+ cell count (current, cells/mm^3)			
<200	41 (25)	59 (56)	<0.001
200–349	28 (17)	18 (17)	
350–499	26 (16)	12 (11)	
≥500	66 (41)	16 (15)	
Currently receiving ART	133 (74)	80 (66)	0.1
Current undetectable viral load (<400 copies/mL)	107 (68)	48 (46)	<0.001
Hepatitis C virus	44 (24)	38 (31)	0.2
Hepatitis B virus	11 (6)	10 (8)	0.5
Diabetes	44 (24)	11 (9)	0.001
Blood pressure (mean, SD)			
Systolic	135 (22)	125 (20)	0.001
Diastolic	81 (11)	78 (13)	0.1
Treated hypertension	81 (45)	35 (29)	0.004

Characteristic	Ischemic stroke, no precipitating infection or drug use N (%)	Ischemic stroke, precipitating infection and/or drug use N (%)	p-value
Lipid levels (mean, SD)			
Total cholesterol (mg/dL)	184 (51)	161 (46)	<0.001
HDL (mg/dL)	44 (17)	40 (16)	0.07
LDL (mg/dL)	104 (39)	93 (38)	0.047
Triglycerides (mg/dL)	195 (167)	167 (99)	0.1
Statin use	60 (33)	17 (14)	<0.001
Smoking	62 (34)	51 (42)	0.2
Kidney function (mL/min/1.73 m^2; mean, SD)	80 (34)	101 (34)	<0.001
BMI (kg/m^2; mean, SD)	27 (6)	25 (5)	0.03
ASCVD risk score (mean, SD)	17 (13)	11 (10)	0.003

ASCVD risk score: 10-year atherosclerotic cardiovascular disease risk as measured by the ASCVD Pooled Cohort Equation; BMI: body mass index; IDU: injection drug user; MSM: men who have sex with men;

Table 3.

Demographic and clinical characteristics of people living with HIV in clinical care at 5 CNICS sites across the U.S. with ischemic stroke by ischemic stroke subtype

Characteristic	Cardioembolic	Large vessel atherosclerosis	Small vessel (Lacunae)	Other	Unknown Subtype	p (CE vs. LVA)	p (CE vs. SV)	p (LVA vs. SV)	P (overall)
N (% of ischemic strokes)	60 (20%)	39 (13%)	72 (24%)	47 (16%)	84 (28%)				
Female sex	18 (30)	8 (21)	20 (28)	8 (17)	28 (34)	0.3	0.8	0.4	0.3
Age (years)						0.4	0.03	0.04	<0.001
<40	11 (18)	8 (21)	3 (4)	19 (40)	17 (20)				
40–49	23 (38)	9 (23)	24 (33)	20 (43)	25 (30)				
50–59	18 (30)	16 (41)	28 (39)	6 (13)	30 (36)				
≥60	8 (13)	6 (15)	17 (24)	2 (4)	12 (14)				
Race/ethnicity						0.2	0.6	0.5	0.3
White	18 (30)	12 (31)	17 (24)	18 (38)	28 (33)				
Black	38 (63)	26 (67)	51 (71)	23 (49)	47 (56)				
Hispanic	4 (7)	0 (0)	3 (4)	5 (11)	9 (11)				
Other	0 (0)	1 (3)	1 (1)	1 (2)	0 (0)				
HIV transmission risk factor						0.048	0.7	0.2	0.3
MSM	14 (23)	16 (41)	18 (25)	17 (36)	25 (20)				
IDU	23 (38)	8 (21)	25 (35)	12 (26)	20 (24)				
Heterosexual	16 (27)	14 (36)	24 (33)	15 (32)	34 (40)				
Other	7 (12)	1 (3)	5 (7)	3 (6)	5 (6)				
CD4+ cell count (nadir, cells/mm^3)						0.6	0.3	0.7	0.2
<200	40 (73)	23 (70)	37 (59)	35 (80)	45 (63)				
200–349	8 (15)	5 (15)	14 (22)	8 (18)	11 (15)				
350–499	4 (7)	1 (3)	4 (6)	1 (2)	9 (13)				
≥500	3 (5)	4 (12)	8 (13)	0 (0)	6 (8)				
CD4+ cell count (current, cells/mm^3)						0.8	0.02	0.2	0.01
<200	24 (44)	12 (36)	13 (21)	24 (55)	27 (38)				
200–349	8 (15)	7 (21)	14 (22)	8 (18)	9 (13)				
350–499	3 (5)	2 (6)	12 (19)	6 (14)	15 (21)				

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Characteristic	Cardioembolic	Large vessel atherosclerosis	Small vessel (Lacunae)	Other	Unknown Subtype	p (CE vs. LVA)	p (CE vs. SV)	p (LVA vs. SV)	P (overall)
≥500	20 (36)	12 (36)	24 (38)	6 (14)	20 (28)				
Currently receiving ART	39 (65)	31 (79)	51 (71)	34 (72)	58 (69)	0.1	0.5	0.3	0.6
Current undetectable viral load (<400 copies/mL)	29 (54)	23 (70)	40 (67)	23 (52)	40 (57)	0.1	0.2	0.8	0.3
Diabetes	11 (18)	8 (21)	17 (24)	5 (11)	14 (17)	0.8	0.5	0.7	0.5
Blood pressure (mean, SD)									
Systolic	126 (19)	133 (16)	140 (23)	121 (19)	131 (23)	0.2	0.004	0.1	0.001
Diastolic	79 (12)	77 (8)	85 (12)	76 (11)	78 (13)	0.6	0.02	0.002	0.006
Treated hypertension	26 (43)	13 (33)	36 (50)	13 (28)	28 (33)	0.3	0.4	0.09	0.08
Lipid levels (mean, SD)									
HDL (mg/dL)	43 (21)	44 (18)	46 (16)	39 (13)	40 (17)	0.9	0.5	0.7	0.2
LDL (mg/dL)	101 (44)	104 (34)	105 (40)	90 (42)	101 (34)	0.8	0.6	0.9	0.5
Total cholesterol (mg/dL)	168 (58)	178 (43)	184 (51)	172 (57)	173 (42)	0.4	0.1	0.6	0.5
Triglycerides (mg/dL)	159 (119)	205 (207)	182 (149)	218 (185)	182 (107)	0.3	0.4	0.6	0.5
Statin use	20 (33)	12 (31)	20 (28)	6 (13)	19 (23)	0.8	0.5	0.7	0.1
Smoking	20 (33)	18 (46)	29 (40)	23 (49)	23 (27)	0.2	0.4	0.6	0.08
Hepatitis C virus	16 (27)	9 (23)	21 (29)	14 (30)	22 (26)	0.7	0.8	0.5	1.0
Hepatitis B virus	5 (8)	2 (5)	2 (3)	3 (6)	9 (11)	0.5	0.2	0.5	0.4
Kidney function (mL/min/1.73m^2; mean, SD)	83 (36)	90 (35)	85 (32)	94 (41)	90 (34)	0.4	0.7	0.5	0.5
BMI (kg/m^2; mean, SD)	24 (5)	25 (5)	27 (5)	24 (5)	28 (8)	0.4	0.006	0.1	0.007
ASCVD risk score (mean, SD)	12 (9)	21 (15)	18 (13)	8 (14)	14 (11)	0.03	0.008	0.5	0.001
Precipitating factors									
Infection	22 (37)	6 (15)	5 (7)	26 (55)	21 (25)	0.02	<0.001	0.2	<0.001
Illicit Drugs	18 (30)	9 (23)	10 (14)	12 (26)	15 (18)	0.5	0.02	0.2	0.2
Infection or Illicit Drugs	30 (50)	13 (33)	13 (18)	34 (72)	32 (38)	0.1	<0.001	0.07	<0.001

ASCVD risk score: 10-year atherosclerotic cardiovascular disease risk as measured by the ASCVD Pooled Cohort Equation; BMI: body mass index; IDU: injection drug user; MSM: men who have sex with men;

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