Types of ischemic strokes among HIV-infected individuals across the United States

H.M. Crane[1], R.M. Nance[1], F. Chow[2], K.J. Becker[1], C.M. Marra[1], J.R. Zunt[1], E.L. Ho[1], R. Kalani[1], A. Huffer[1], G. Burkholder[3], R.D. Moore[4], W.C. Mathews[5], J.J. Eron[6], D.R. Drozd[1], M.S. Saag[3], M.M. Kitahata[1], J.A.C. Delaney[1], D.L. Tirschwell[1]

[1]University of Washington, Seattle, WA; [2]University of California San Francisco, San Francisco, CA; [3]University of Alabama Birmingham, Birmingham, AL; [4]Johns Hopkins University, Baltimore, MD; [5]University of California San Diego, San Diego, CA; [6]University of North Carolina, Chapel Hill, NC

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Contact:
Heidi Crane, MD, MPH
University of Washington
Email: hcrane@uw.edu

Table 1. Clinical & demographic characteristics by ischemic stroke subtype

Characteristic	Cardioembolic N=76 N (%)	Atheroembolic N=59 N (%)	Small vessel (Lacunae) N=79 N (%)	Other/Unknown N=39 N (%)	P-value
Sex					0.9
Male	55 (72)	43 (73)	58 (73)	31 (79)	
Female	21 (28)	16 (27)	21 (27)	8 (21)	
Age, years					0.009
<40	16 (21)	11 (19)	6 (8)	14 (36)	
40-49	25 (33)	17 (29)	30 (38)	17 (44)	
50-59	22 (29)	22 (37)	30 (38)	7 (18)	
≥60	13 (17)	9 (15)	13 (16)	1 (3)	
Race/Ethnicity					0.4
White	20 (26)	24 (41)	24 (20)	13 (33)	
African-American	49 (64)	32 (54)	50 (63)	20 (51)	
Hispanic	7 (9)	2 (3)	4 (5)	5 (13)	
Other/unknown	0 (0)	1 (2)	1 (1)	1 (3)	
HIV Transmission Risk Factor					0.2
Men who have sex with men	19 (25)	22 (37)	24 (32)	13 (33)	
Heterosexual	23 (30)	24 (41)	25 (33)	16 (41)	
Injection drug use	27 (36)	11 (19)	23 (31)	6 (15)	
Other/unknown	7 (9)	2 (3)	3 (4)	4 (10)	
CD4 count closest to event (cells/µl)					0.5
0-200	28 (41)	17 (33)	23 (32)	14 (48)	
201-350	14 (20)	9 (17)	16 (23)	2 (7)	
>350	27 (39)	26 (50)	32 (45)	13 (45)	
HIV-1 RNA closest to event					0.6
<400	36 (52)	36 (69)	43 (61)	16 (53)	
400-10,000	9 (13)	6 (12)	9 (13)	5 (17)	
10,000-100,000	13 (19)	5 (10)	12 (17)	3 (10)	
≥100,000	11 (16)	5 (10)	6 (9)	6 (20)	
Diabetes					0.4
No	59 (78)	50 (85)	63 (80)	35 (90)	
Yes	17 (22)	9 (15)	16 (20)	4 (10)	
Blood pressure mean (mean, SD)					0.02
Systolic (mmHg)	129 (20)	130 (19)	138 (22)	123 (21)	
Anti-hypertensive medication					0.09
No	47 (62)	38 (64)	42 (53)	30 (77)	
Yes	29 (38)	21 (36)	37 (47)	9 (23)	
Lipid Levels mean (mean, SD)					
HDL (mg/dL)	46 (21)	44 (17)	44 (15)	38 (12)	0.4
Total Cholesterol (mg/dL)	168 (49)	183 (54)	196 (58)	173 (46)	0.03
Triglycerides (mg/dL)	164 (134)	193 (183)	197 (163)	163 (87)	0.6
Statin use					0.3
No	61 (80)	52 (88)	66 (84)	36 (92)	
Yes	15 (20)	7 (12)	12 (16)	3 (8)	
Smoking					1
No	47 (62)	37 (63)	49 (62)	24 (62)	
Yes	29 (38)	22 (37)	30 (38)	15 (38)	
Body mass index (mean, SD)					
BMI (kg/m2)	24 (5)	25 (6)	27 (6)	26 (7)	0.1
Risk Score (mean, SD)					
Framingham CHD (% 10 year event risk)	13 (12)	17 (15)	17 (13)	8 (10)	0.06

Background

- Stroke rates are higher among persons living with HIV (PLWH)
- Strokes are becoming more common in PLWH, likely due to chronological aging of the population, increased rates of age-related comorbidities such as diabetes and hypertension, cumulative exposure to HIV-related inflammation and immune activation, and possibly metabolic impacts of specific antiretroviral medications
- Large studies are lacking that examined strokes in PLWH and included strokes types and subtypes in the current antiretroviral therapy (ART) treatment era
- Many prior studies of strokes in HIV have often used unadjudicated or unverified stroke outcomes, could not distinguish hemorrhagic from ischemic strokes, were conducted early in the ART treatment era or preART, included stroke as a composite outcome with cardiovascular disease (CVD) and/or death
- Most of the evidence for an increased risk of CVD in HIV is from studies of myocardial infarction. Estimates of stroke risk are less well-defined, in part because of the lack of a standard approach to identifying stroke in HIV
- We developed and implemented a stroke adjudication protocol in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS), a large and diverse cohort of PLWH
- We conducted this study to characterize stroke events by type (ischemic vs. hemorrhagic) and ischemic subtypes, and to identify predisposing causes

Table 2. Predisposing causes of ischemic stroke by stroke subtype

Characteristic	Cardioembolic N=76 N (%)	Atheroembolic N=59 N (%)	Small vessel (Lacunae) N=79 N (%)	Other/Unknown N=39 N (%)	P-value
CNS infection	27 (36)	14 (24)	10 (13)	17 (44)	0.001
Illicit drug use	22 (29)	11 (19)	13 (16)	8 (21)	0.3
CNS infection or illicit drug use	38 (50)	22 (37)	21 (27)	23 (59)	0.002

Methods

- The CNICS cohort includes PLWH receiving care at 8 clinical sites across the United States
- The CNICS data repository integrates comprehensive clinical data from all outpatient and inpatient encounters; these data include diagnoses, laboratory test results; medications; and procedures codes such as cerebral angiography
- Individuals who had a potential incident stroke event from 5 sites were included in these analyses
- Stroke ascertainment: Using comprehensive diagnosis and procedure codes, we identified potential stroke events
- For every potential stroke event identified, sites assembled and uploaded a standardized set of clinical information including neurology and other provider notes and neuroimaging for centralized review
- Stroke adjudication: Two neurologists reviewed each packet, followed by a 3rd if discrepancies occurred
- Each neurologist identified stroke type, subtype and whether the stroke was associated with CNS infection or illicit drug use. Criteria used to classify potential stroke events included signs and symptoms, symptom duration, and clinical imaging
- Ischemic stroke subtypes (e.g. small vessel, cardioembolic, atheroembolic) were based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria
- We used Chi-squared tests for categorical variables and t-tests for continuous variables to assess differences in demographic and clinical characteristics, including those related to HIV and CVD risk, among individuals by stroke type and subtype

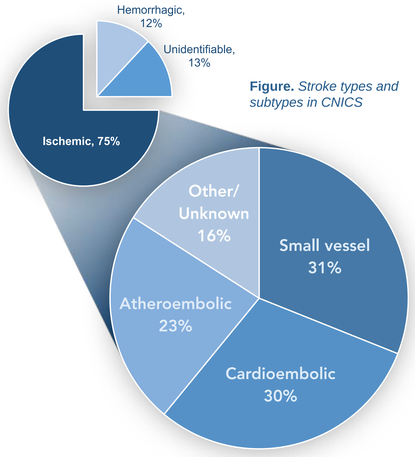


Figure. *Stroke types and subtypes in CNICS*

Results

- Among 23,189 PLWH, 339 had a stroke, 253 (75%) of which were ischemic (Figure)
- Cardioembolic and small vessel were the most common ischemic stroke subtypes (Figure)
- Compared with individuals with small vessel strokes, those with cardioembolic strokes were younger (21% vs. 8% <40 years, p<0.01) (Table 1) and more likely to be associated with illicit drug use or CNS infection (50% vs. 27%, p<0.01) (Table 2)
- Small vessel strokes were associated with use of antihypertensive medications, higher systolic blood pressure (mean 138 vs. 129 or 130 mmHg, p=0.02), and higher total cholesterol (mean 196 vs. 168 or 183 mg/dL, p=0.03) compared to those with cardioembolic or atheroembolic stroke respectively (Table 1)
- 41% of ischemic strokes occurred in the setting of illicit drug use or CNS infection

Strengths

- To our knowledge this is the largest study to date describing strokes in PLWH in the setting of comprehensive clinical data, with carefully adjudicated outcomes based on primary data
- Adjudication facilitates capturing stroke type and subtypes as well as potential predisposing factors
- The CNICS cohort provides geographic, racial/ethnic, and clinical diversity

Limitations

- We did not have comprehensive clinical information on OTC medications such as aspirin use
- We focused on clinically relevant strokes therefore would miss those with subtle clinical symptoms that the patient and providers failed to recognize
- We also would not capture strokes that resulted in death before hospitalization and therefore did not undergo any evaluation

Conclusions

- Ischemic stroke, particularly small vessel and cardioembolic subtypes are most common in HIV
- A high proportion of ischemic and particularly cardioembolic strokes were related to illicit drug use or infection
- Rigorous stroke type and subtype definitions allowed for clear elucidation of traditional and non-traditional risk factors associated with stroke types which will better inform interventions designed to improve clinical management and reduce risk

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