Title

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Authors

Chow, Felicia C
Wilson, Michael R
Wu, Kunling
et al.

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Stroke incidence is highest in women and non-Hispanic blacks living with HIV in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort

Felicia C. Chow[a,b,*], Michael R. Wilson[a,c,*], Kunling Wu[d], Ronald J. Ellis[e], Ronald J. Bosch[d] and Benjamin P. Linas[f]

Objective: To investigate the incidence of first-ever stroke/transient ischemic attack (TIA) and associated risk factors in a cohort of persons living with HIV infection (PLWH).

Design: Observational cohort study

Methods: We determined incidence rates of first-ever stroke/TIA in PLWH after ART initiation from the AIDS Clinical Trials Group ALLRT cohort and its parent trials. Poisson regression models evaluated baseline and time-varying covariates as risk factors for stroke/TIA.

Results: The incidence rate of stroke/TIA was 1.69 per 1000 person-years. Incidence rates were highest in women (2.88 stroke/TIAs per 1000 person-years compared with 1.40 per 1000 person-years in men) and non-Hispanic Blacks (2.51 stroke/TIAs per 1000 person-years compared with 0.77 per 1000 person-years in Hispanic/other race/ethnicities and 1.56 per 1000 person-years in whites). In a multivariable model, we found a significant age-by-sex interaction ($P = 0.01$). The higher risk of stroke/TIA in women was more pronounced at younger ages, whereas older age conferred a greater increase in stroke/TIA risk in men than women. Other risk factors for stroke/TIA included hypertension, higher LDL, and HIV RNA greater than 200 copies/ml. Overweight/obese BMI and higher $CD4^+$:$CD8^+$ ratio protected against stroke/TIA.

Conclusion: Women and non-Hispanic Blacks living with HIV had the highest incidence rates of stroke/TIA. A concerted effort must be made to include PLWH from these at-risk groups in observational and interventional studies aimed at understanding stroke mechanisms and reducing stroke risk in HIV infection. Strategies to modify stroke risk in PLWH should employ a multipronged approach targeting vascular risk factors and engaging and retaining patients in HIV care.

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Keywords: cardiovascular risk, cerebrovascular disease, HIV infection, race disparities, sex disparities, stroke, transient ischemic attack

Introduction

Although rates of stroke are higher in persons living with HIV infection (PLWH) compared with age-matched HIV-uninfected individuals, many questions persist regarding the nature of cerebrovascular disease and associated risk factors in HIV infection. Several large observational cohort studies have demonstrated that HIV confers an increased risk of stroke, independent of traditional vascular risk factors [1–5]. The majority of

[a]Weill Institute for Neurosciences, [b]Department of Neurology and Division of Infectious Diseases, [c]Department of Neurology, University of California, San Francisco, California, [d]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, [e]Departments of Neurosciences and Psychiatry, University of California, San Diego, California, and [f]Department of Medicine, Division of Infectious Diseases, Boston University, Boston, Massachusetts, USA.

Correspondence to Felicia C. Chow, MD, MAS, University of California, San Francisco at Zuckerberg San Francisco General Hospital, 1001 Potrero Avenue, Building 1, Room 101, San Francisco, CA 94110, USA.

E-mail: felicia.chow@ucsf.edu

* Felicia C. Chow and Michael R. Wilson contributed equally to this work.

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these studies have relied on administrative and billing codes to define stroke outcomes from electronic medical records. Furthermore, most studies were performed using clinical care databases or clinic-based cohorts for which information on stroke and other covariates was not assessed at regular intervals or following a standardized protocol, potentially resulting in incomplete or inaccurate capture of clinical information.

We leveraged the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort and its parent trials to investigate incident first-ever stroke and associated risk factors in PLWH. One key strength of ALLRT is that participants were followed at regular intervals over an extended observation period and underwent standardized collection of clinical and laboratory data, including stroke events. In addition, we capitalized on the relative diversity of ALLRT to explore sex and race differences in stroke risk, based on data from other cohort studies suggesting that the additional vascular risk conferred by HIV infection may be greater in women [1,6,7] and individuals of non-white race/ethnicity [4,5].

Methods

Study population

We conducted a prospective study of antiretroviral (ART)-naive PLWH enrolled in an ACTG trial between June 1998 and June 2011. Seven thousand and seventy-three participants were randomized to receive ART in one of several ACTG parent trials (ACTG protocol 384, 388, A5014, A5095, A5142, A5202, A5257), of which 4732 continued in ALLRT at their conclusion [8]. Participants were followed a minimum of once every 12 weeks until the completion of the parent protocol and every 16 weeks thereafter in ALLRT. We excluded individuals with a history of stroke at baseline and those who did not initiate ART or did not contribute follow-up time.

Study outcomes

We defined the primary outcome as a composite of first-ever stroke or transient ischemic attack (TIA) identified prospectively at study follow-up visits through a centralized reporting system. TIA was defined as a focal neurologic deficit lasting greater than 30 s but less than 24 h with rapid evolution of symptoms to maximal deficit in less than 5 min followed by complete resolution; no immediately preceding head trauma; and no associated symptoms of seizure or migraine. Strokes were confirmed by either a demonstrable acute stroke on brain imaging or rapid onset of a focal neurologic deficit persisting for at least 24 h and attributable to arterial obstruction or rupture in the absence of other causes.

Covariates

We collected data on the following time-varying variables: hypertension, defined as SBP greater than 140 mmHg or DBP greater than 90 mmHg irrespective of antihypertensive therapy use; low-density lipoprotein (LDL) cholesterol level, dichotomized as less than or greater than or equal to 160 mg/dl; myocardial infarction and diabetes mellitus; current or prior smoker; hepatitis C virus (HCV) infection, defined by an existing diagnosis in ALLRT or a positive HCV antibody; BMI, categorized as underweight ($<18.5\,kg/m^2$), normal ($18.5-24\,kg/m^2$), overweight ($25-30\,kg/m^2$), and obese ($>30\,kg/m^2$); waist circumference, classified as increased when greater than 102 cm for men and greater than 88 cm for women; waist-to-hip ratio classified as increased when greater than or equal to 0.90 for men and greater than or equal to 0.85 for women; and renal dysfunction, defined as an estimated glomerular filtration rate less than $60\,ml/min/1.73\,m^2$ using the Chronic Kidney Disease Epidemiology Collaboration equation. Statin use (in the preceding 12 months) was available for ALLRT participants. Injection drug use was defined at baseline as never, current, or previous use.

We also noted time-varying history of several central nervous system (CNS) opportunistic infections/malignancies, including toxoplasmosis, progressive multifocal leukoencephalopathy, and lymphoma. We collected baseline and time-varying $CD4^+$ count, $CD4^+$ to $CD8^+$ ratio dichotomized as less than 0.32 and greater than or equal to 0.32 [9], and HIV RNA level. In addition, we examined ART use (in the preceding 12 months) by class [protease inhibitor; nonnucleoside reverse transcriptase inhibitor (NNRTI); nucleoside reverse transcriptase inhibitor (NRTI); and integrase inhibitor use]. We also evaluated abacavir and atazanavir use separately from NRTI and protease inhibitor use given evidence supporting an association with (abacavir) and protective effect against (atazanavir) cardiovascular disease [3,10–12].

Statistical analysis

Participant characteristics were compared between groups using Wilcoxon rank-sum and chi-square tests. First-ever stroke/TIA incidence rates per 1000 person-years were calculated overall and after stratification by age, sex, and race/ethnicity. We performed unadjusted Poisson regression models with each individual baseline and time-varying covariate to identify risk factors for incident stroke/TIA. We then constructed age-adjusted Poisson models followed by models adjusted for age in addition to sex and race/ethnicity. Given the modest number of incident stroke events, we built a multivariable model (Model 1) using forward stepwise selection with strict inclusion and exclusion criteria ($P \leq 0.05$ for retention in the model, $P > 0.10$ for removal from the model). In a second multivariable model (Model 2), we forced the inclusion of two variables into Model 1 that were not retained in the forward stepwise selection (diabetes mellitus and smoking) but had face validity as established factors that impact stroke risk. We collapsed underweight and normal BMI and overweight and obese BMI, creating a two-level variable for BMI that

performed similarly to a four-level variable in a sensitivity analysis. Missing data for each variable were represented in the analyses as missing value categories.

Out of concern for the reliability of TIA diagnoses, we performed a sensitivity analysis excluding TIAs from the outcome. In addition, based on the results of the unadjusted and adjusted models, we checked for several potential statistical interactions, including differences in the association of: age, race, BMI, smoking, and HIV viral load with stroke risk by sex; BMI with stroke risk by smoking status; age with stroke risk by lower vs. higher BMI; and protease inhibitor use with stroke risk in the time period before and after 2005. To address the potential for model overfitting, we constructed a simplified, more parsimonious multivariable model that included: sex, an age-by-sex interaction, hypertension, and BMI.

Results

Study enrollment

Of the 7073 PLWH enrolled in an ACTG parent trial, we excluded 45 because of a history of stroke at baseline and another 95 participants who did not initiate ART or did not contribute follow-up time. Of the 45 excluded individuals with a history of stroke at baseline, 15 were women and 30 men, resulting in a higher prevalence of a history of stroke at baseline among women (1.1% for women vs. 0.5% for men, $P = 0.023$). A total of 6933 participants were included in the analysis. The median duration of observation was 3.4 years [interquartile range (IQR) 2.4–6.4].

Demographic and clinical characteristics at entry into the parent trial

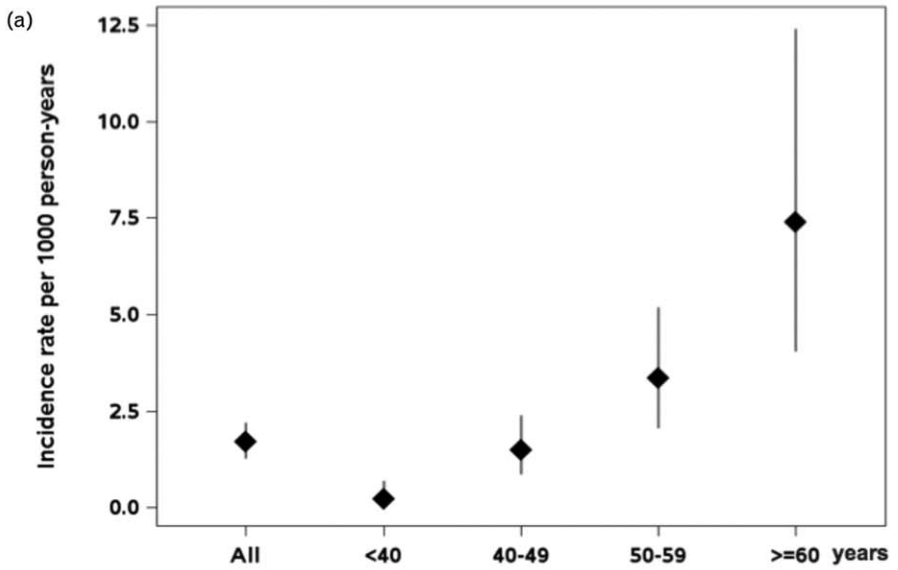
Baseline demographic and clinical characteristics are shown in Table 1. Of 6933 participants, 20% were women, 37% were non-Hispanic Blacks, and 21% were Hispanic. The median age at baseline was 37 years, and 12% of participants were at least 50 years. Prior to initiating ART, the median $CD4^+$ count was 243 cells/μl and median HIV RNA was 57 624 copies/ml. Over the total person-years of observation, HIV RNA was suppressed (<200 copies/ml) 85% of the time for the entire cohort (85% for men, 83% for women). The majority of participants (91%) had no history of injection drug use.

Table 1. Demographics and clinical characteristics at the time of entry into the ALLRT cohort parent trials prior to initiation of antiretroviral therapy.

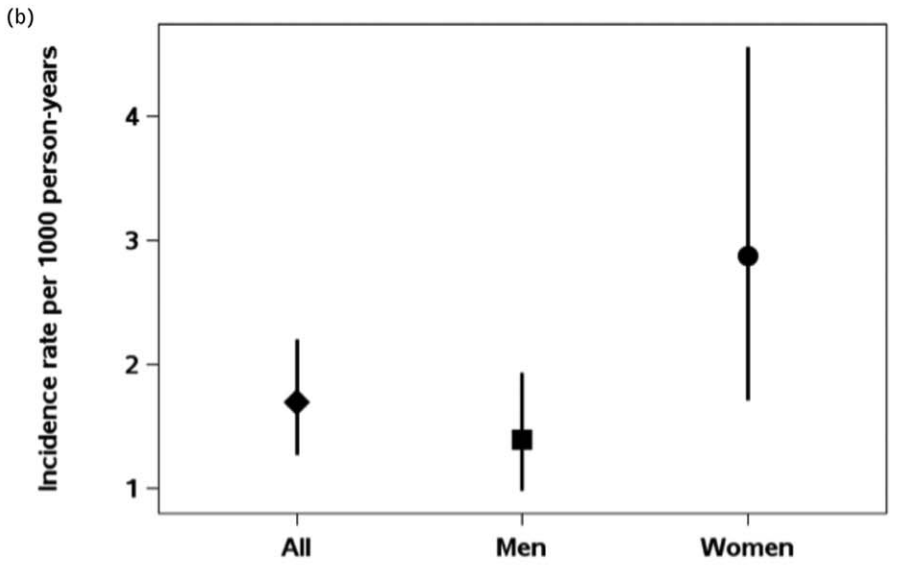
	All ($n = 6933$)	Men ($n = 5563$)	Women ($n = 1370$)	P value[a]
Demographics				
Women, n (%)	1370 (20)	–	–	–
Age (years), median (IQR)	37 (30–44)	37 (30–44)	38 (31–46)	<0.001
Race/ethnicity, *n* (%)				
White, non-Hispanic	2749 (40)	2479 (45)	270 (20)	<0.001
Black, non-Hispanic	2536 (37)	1768 (32)	768 (56)	
Hispanic (regardless of race)	1452 (21)	1149 (21)	303 (22)	
Asian/Pacific Islander	116 (2)	106 (2)	10 (1)	
American Indian or Alaskan Native	33 (<1)	25 (<1)	8 (1)	
More than one race/unknown	47 (<1)	36 (<1)	11 (1)	
Vascular and other risk factors				
Hypertension, *n* (%)[b]	819 (12)	649 (12)	170 (12)	0.72
LDL≥160 mg/dl, *n* (%)[b]	143 (2)	100 (2)	43 (3)	0.003
Diabetes mellitus, *n* (%)	245 (4)	154 (3)	91 (7)	<0.001
Myocardial infarction, *n* (%)	42 (1)	33 (1)	9 (1)	0.79
Renal dysfunction, *n* (%)	109 (2)	70 (1)	39 (3)	<0.001
Smoking status, *n* (%)[b]				
Never	2174 (31)	1682 (30)	492 (36)	<0.001
Current	975 (14)	771 (14)	204 (15)	
Previous	1949 (28)	1624 (29)	325 (24)	
HCV infection, *n* (%)	392 (6)	298 (5)	94 (7)	0.031
BMI, *n* (%)[b]				
Underweight/normal (<24 kg/m^2)	3654 (53)	3096 (56)	558 (41)	<0.001
Overweight (25–30 kg/m^2)	2105 (30)	1743 (31)	362 (26)	
Obese (>30 kg/m^2)	1081 (16)	646 (12)	435 (32)	
HIV factors and health-related behaviors				
$CD4^+$ count (cells/μl), median (IQR)	243 (89–370)	243 (87–371)	244 (103–367)	0.70
HIV RNA (copies/ml), median (IQR)	57 624 (21 430–203 256)	61 373 (23 966–218 058)	42 655 (12 666–138 095)	<0.001
Intravenous drug use, *n* (%)				
Never	6303 (91)	5035 (91)	1268 (93)	0.053
Current	18 (<1)	16 (<1)	2 (<1)	
Previous	612 (9)	512 (9)	100 (7)	

BMI, body mass index; HCV, hepatitis C virus; IQR, interquartile range; LDL, low-density lipoprotein.
[a]Comparing men and women by Wilcoxon rank-sum or chi-square tests.
[b]Data missing at entry for hypertension in 30% overall (30% of men, 30% of women); for LDL greater than or equal 160 in 21% overall (21% of men, 19% of women); for smoking in 26% overall (27% of men, 25% of women); for BMI in 1% overall (1% of men, 1% of women).

The race/ethnicity distribution between women and men was statistically different, with fewer non-Hispanic white women and more non-Hispanic black women compared with men (Table 1). Women were also slightly older (median 38 vs. 37 years, $P < 0.001$) and had a higher proportion of several vascular risk factors at baseline (Table 1). There was no statistically significant difference in CD4$^+$ cell count prior to initiation of ART by sex, but women had a lower HIV RNA (median 42 655 vs. 61 373 copies/ml, $P < 0.001$).

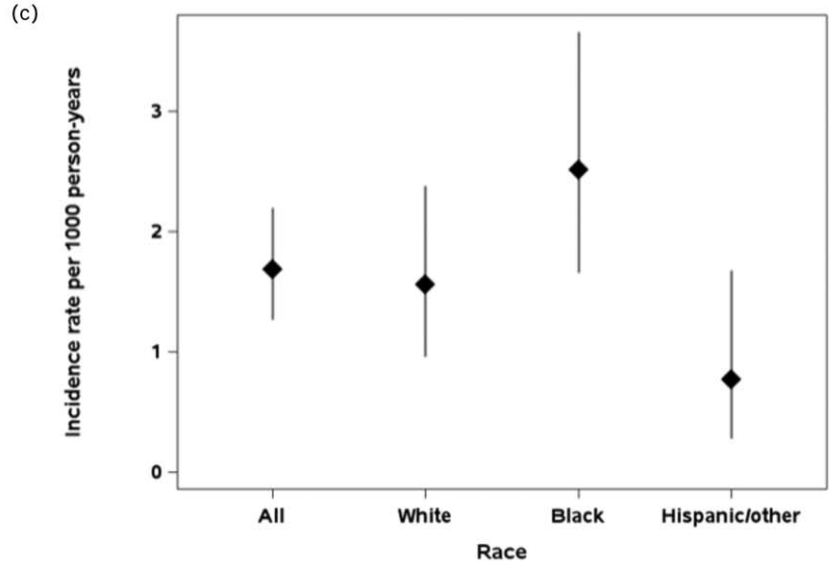


No. of strokes	54	3	17	20	14
Person-years	32,023	12,780	11,396	5,954	1,893
Rate (per 1000 PY)	**1.69** (1.27-2.20)	**0.23** (0.05-0.69)	**1.49** (0.87-2.39)	**3.36** (2.05-5.19)	**7.39** (4.04-12.41)

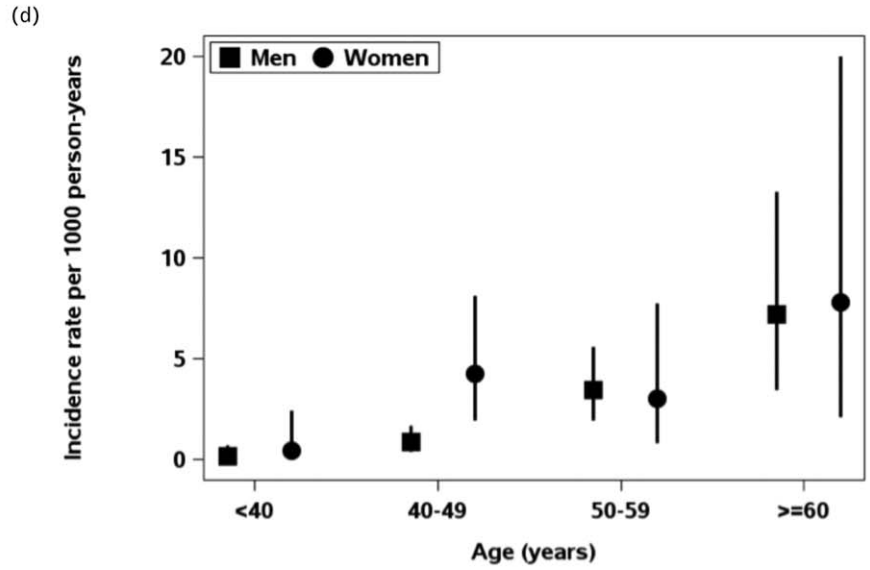


No. of strokes	54	36	18
Person-years	32,023	25,871	6,242
Rate (per 1000 PY)	**1.69** (1.27-2.20)	**1.40** (0.98-1.93)	**2.88** (1.71-4.56)

Fig. 1. Rates of stroke/transient ischemic attack with 95% confidence intervals by time-updated age, sex, and race/ethnicity. (a) Rates of stroke/TIA with 95% confidence intervals by time-updated age group. (b) Rates of stroke/TIA with 95% confidence intervals by sex. (c) Rates of stroke/TIA with 95% confidence intervals by race/ethnicity. (d) Rates of stroke/TIA with 95% confidence intervals by time-updated age and sex. TIA, transient ischemic attack.



No. of strokes	54	21	27	6
Person-years	32,023	13,497	10,743	7,784
Rate (per 1000 PY)	**1.69** (1.27-2.20)	**1.56** (0.96-2.38)	**2.51** (1.66-3.66)	**0.77** (0.28-1.68)



No. of strokes	M: 2	F: 1	M: 8	F: 9	M: 16	F: 4	M: 10	F: 4
Person-years	10,473	2,307	9,291	2,106	4,636	1,317	1,381	512
Rate (per 1000 PY)	**0.19** (0.02-0.69)	**0.43** (0.01-2.41)	**0.86** (0.37-1.70)	**4.27** (1.95-8.11)	**3.45** (1.97-5.60)	**3.04** (0.83-7.77)	**7.24** (3.47-13.31)	**7.81** (2.13-20.01)

Fig. 1. (Continued).

Stroke/transient ischemic attack rates overall and stratified by age, sex, and race/ethnicity

Fifty-four stroke/TIAs occurred over 32 023 person-years (Fig. 1), for an overall incidence rate of 1.69 per 1000 person-years. The median years since initiation of ART at the time of stroke was 4.0 [interquartile range (IQR) 1.9–6.7]. The risk of stroke/TIA was not significantly different between the first half (1998–2004) and second half (2005–2013) of the observation period. The incidence rate of stroke/TIA rose with older age, with 0.23 stroke/TIAs per 1000 person-years for those less than 40 years and 7.39 per 1000 person-years for those 60 years or older at the time of incident stroke (Fig. 1). The incidence of stroke/TIA was higher in women compared with men overall [2.88 per 1000 person-years vs. 1.40 per 1000 person-years, relative risk (RR) 2.07, 95% CI 1.17–3.63, $P = 0.01$] and across all race/ethnicity groups. The age-adjusted RR of

Table 2. Unadjusted and adjusted relative risk of stroke/transient ischemic attack associated with demographics, vascular, and HIV-related factors in the ALLRT cohort and its parent trials.

	Unadjusted model		Age-adjusted		Model 1[a]		Model 2[b]	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Female sex	2.07 (1.17–3.63)	0.01	1.72 (0.96–3.09)	0.07	1.94 (1.03–3.66)[c]	0.04	1.96 (1.04–3.67)[c]	0.04
Current age (per 10 year increase)	2.43 (2.03–2.91)	<0.001	–	–	–	–	–	–
For women	1.80 (1.35–2.40)	<0.001	–	–	1.49 (1.07–2.09)	0.02	1.47 (1.04–2.08)	0.03
For men	2.73 (2.19–3.41)	<0.001	–	–	2.44 (1.88–3.17)	<0.001	2.35 (1.79–3.10)	<0.001
Race/ethnicity (vs. non-Hispanic Black)								
Hispanic and other	0.31 (0.13–0.74)	0.009	0.34 (0.14–0.82)	0.02	0.44 (0.18–1.09)	0.08	0.45 (0.18–1.09)	0.08
Non-Hispanic White	0.62 (0.35–1.09)	0.1	0.60 (0.34–1.05)	0.08	0.87 (0.46–1.64)	0.7	0.90 (0.47–1.72)	0.7
Hypertension	5.22 (3.03–9.02)	<0.001	3.67 (2.06–6.56)	<0.001	3.64 (2.04–6.48)	<0.001	3.51 (1.98–6.22)	<0.001
LDL≥160 mg/dl	2.74 (1.34–5.63)	0.006	2.29 (1.11–4.75)	0.03	2.41 (1.13–5.12)	0.02	2.47 (1.15–5.31)	0.02
Diabetes mellitus	3.01 (1.42–6.36)	0.004	1.50 (0.68–3.30)	0.3	–	–	1.57 (0.69–3.57)	0.3
Myocardial infarction	1.32 (0.18–9.62)	0.8	0.54 (0.07–4.12)	0.6	–	–	–	–
Renal dysfunction	4.79 (2.61–8.79)	<0.001	2.05 (1.03–4.10)	0.04	1.90 (0.98–3.69)	0.06	1.93 (1.00–3.74)	0.05
Statin use prior 12 months	2.17 (1.13–4.17)	0.02	1.20 (0.60–2.39)	0.6	–	–	–	–
Current/prior smoker (vs. never)	2.03 (1.08–3.82)	0.03	1.74 (0.93–3.25)	0.08	–	–	1.53 (0.83–2.84)	0.2
Current/prior injection drug use (vs. never)	1.22 (0.49–3.04)	0.7	1.08 (0.43–2.70)	0.9	–	–	–	–
HCV infection	1.86 (0.84–4.12)	0.1	1.37 (0.62–3.03)	0.4	–	–	–	–
Overweight/obese BMI (vs. underweight/normal BMI)	0.60 (0.35–1.03)	0.06	0.54 (0.31–0.92)	0.02	0.43 (0.25–0.74)	0.002	0.43 (0.25–0.75)	0.003
Waist circumference >102 cm for men, >88 cm for women	1.48 (0.80–2.77)	0.2	1.11 (0.58–2.10)	0.8	–	–	–	–
Waist-to-hip ratio ≥0.90 for men, ≥0.85 for women	1.78 (0.78–4.03)	0.2	1.08 (0.46–2.52)	0.9	–	–	–	–
Baseline $CD4^+$ count <200 cells/μl (vs. ≥200 cells/μl)	1.34 (0.79–2.29)	0.3	1.16 (0.68–1.98)	0.6	–	–	–	–
Time-varying $CD4^+$ count <200 cells/μl (vs. ≥200 cells/μl)	2.22 (1.14–4.30)	0.02	2.42 (1.24–4.74)	0.01	–	–	–	–
Baseline $\log_{10}$ HIV RNA (per 1 $\log_{10}$ increase)	0.78 (0.54–1.14)	0.2	0.71 (0.48–1.05)	0.08	–	–	–	–
Time-varying HIV RNA >200 copies/ml (vs. ≤200 copies/ml)	2.33 (1.30–4.18)	0.005	3.11 (1.71–5.64)	<0.001	2.23 (1.19–4.16)	0.01	2.19 (1.16–4.10)	0.01
Time-varying $CD4^+$:$CD8^+$ ratio ≥0.32 (vs. <0.32)	0.42 (0.24–0.73)	0.002	0.39 (0.22–0.69)	0.001	0.49 (0.27–0.87)	0.01	0.49 (0.27–0.88)	0.02
Protease inhibitor use prior 12 months	1.71 (0.98–2.97)	0.06	1.80 (1.03–3.14)	0.04	–	–	–	–
NRTI use prior 12 months	0.39 (0.18–0.87)	0.02	0.46 (0.20–1.04)	0.06	–	–	–	–
NNRTI use prior 12 months	0.85 (0.50–1.45)	0.6	0.76 (0.45–1.30)	0.3	–	–	–	–
Integrase inhibitor use prior 12 months	1.47 (0.63–3.44)	0.4	1.46 (0.62–3.42)	0.4	–	–	–	–
Atazanavir use prior 12 months	1.14 (0.61–2.13)	0.7	1.22 (0.66–2.28)	0.5	–	–	–	–
Abacavir use prior 12 months	1.16 (0.63–2.13)	0.6	1.14 (0.62–2.10)	0.7	–	–	–	–

BMI, body mass index; HCV, hepatitis C virus; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.
[a]Model 1 adjusted for all variables shown in the column and age-by-sex interaction ($P = 0.01$).
[b]Model 2 adjusted for all variables in Model 1, including age-by-sex interaction ($P = 0.02$), diabetes mellitus and smoking.
[c]Relative risk shown for female sex in Models 1 and 2 is at 50 years of age.

stroke/TIA for women was 1.72 (95% CI 0.96–3.09, $P = 0.07$; Table 2). Incidence of stroke/TIA in Hispanics combined with other race/ethnicities was 0.77 compared with 2.51 per 1000 person-years in non-Hispanic Blacks (age-adjusted RR 0.34, 95% CI 0.14–0.82, $P = 0.02$) and 1.56 per 1000 person-years in whites (age-adjusted RR 0.60, 95% CI 0.34–1.05, $P = 0.08$; Fig. 1 and Table 2).

Vascular risk and HIV-related risk factors for stroke/transient ischemic attack

In age-adjusted analyses, several variables were associated with a higher RR of stroke/TIA (Table 2). Of vascular risk factors, hypertension was associated with the highest risk of stroke/TIA with a RR of 3.67 (95% CI 2.06–6.56). An LDL greater than or equal to 160 mg/dl more than doubled the risk of stroke/TIA, as did renal dysfunction. Although being a smoker was associated with an increased risk of stroke/TIA in an unadjusted model, this association no longer reached statistical significance after adjusting for age (Table 2). In age-adjusted models, we also did not observe a statistically significant association between diabetes mellitus, injection drug use, and HCV infection on stroke/TIA risk. Having an overweight/obese BMI was protective against stroke/TIA (RR 0.54, 95% 0.31–0.92, $P = 0.02$).

Among HIV-related risk factors, recent viremia (HIV RNA >200 copies/ml) conferred over three-fold higher risk of stroke/TIA (age-adjusted RR 3.11, 95% CI 1.71–5.64). A recent $CD4^+$ count less than 200 cells/μl was associated with over twice the risk of stroke/TIA, while a $CD4^+$ to $CD8^+$ ratio greater than or equal to 0.32 was associated with a 60% reduction in stroke/TIA risk (Table 2). Results were similar when analyzing continuous $CD4^+$:$CD8^+$ ratio (age-adjusted RR 0.52 per 0.5 units higher, 95% CI 0.34–0.78, $P = 0.002$). Use of a protease inhibitor was also a risk factor for stroke/TIA in

an age-adjusted model, although it was not retained in the final multivariable model. We did not find a statistically significant association of abacavir or atazanavir use with stroke/TIA risk.

We observed a statistically significant interaction between age and sex on stroke risk, which we included in age, sex, and race-adjusted models. The addition of sex, race, and an age-by-sex interaction term did not appreciably change the RR point estimates compared with the models adjusted only for age for most of the vascular and HIV-related covariates (Supplemental Table, http://links.lww.com/QAD/B244).

In a multivariable model adjusted for age, sex, an age-by-sex interaction term, race/ethnicity, LDL level, hypertension, diabetes mellitus, BMI, smoking, renal dysfunction, time-varying HIV RNA level and $CD4^+$ to $CD8^+$ ratio (Model 1), older age was associated with a higher risk of stroke/TIA for women and men, although the effect of age was greater for men (RR 2.44 for every 10 years for men, 95% CI 1.88–3.17 vs. RR 1.49 for every 10 years for women, 95% CI 1.07–2.09). At close to the median age when stroke/TIAs occurred (50 years), women had almost twice the stroke/TIA risk compared with men (RR 1.94, 95% CI 1.03–3.66). At younger ages, the higher risk in women was even more pronounced. For example, at 40 years of age, women had over three times the stroke/TIA risk compared with men (RR 3.17, 95% CI 1.45–6.93). We observed a trend toward Hispanic combined with other race/ethnicities being protective against stroke/TIA compared with non-Hispanic black race/ethnicity. Of vascular risk factors, hypertension, LDL greater than or equal to 160 mg/dl, and renal dysfunction conferred greater risk of stroke/TIA, whereas overweight/obese BMI was associated with a lower risk of stroke/TIA (Table 2 and Fig. 2). Of HIV-related factors, recent HIV RNA greater than 200 copies/ml was a risk factor for stroke/TIA, whereas a $CD4^+$ to $CD8^+$ ratio at least 0.32 was associated with a lower risk of stroke/TIA. Forced inclusion of diabetes mellitus and smoking (Model 2) did not significantly impact the associations observed in Model 1.

Sensitivity analyses

In a sensitivity analysis restricted to strokes ($n = 41$), the results of the multivariable model were comparable with when TIAs were included, although the estimated effect of certain risk factors (e.g. female sex at 50 years of age, LDL $\geq$160 mg/dl) no longer reached statistical significance. None of the interactions that we tested for were statistically significant aside from the interaction between age and sex on stroke risk, which was included in the multivariable models (Table 2). Results from a simplified, more parsimonious multivariable model that included sex, an age-by-sex interaction, hypertension, and BMI (Supplemental Table, http://links.lww.com/QAD/

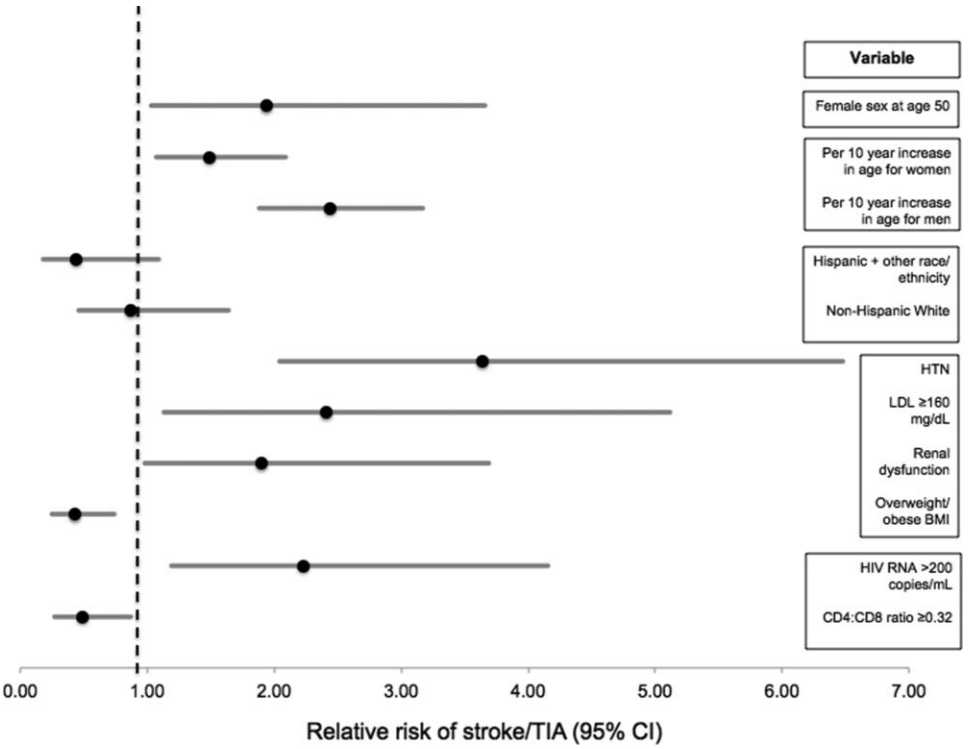


Fig. 2. Multivariable model of relative risk of stroke/transient ischemic attack in ALLRT cohort. Model adjusted for all variables shown in the figure and age-by-sex interaction.

B244) were highly comparable with the full multivariable models (Models 1 and 2 from Table 2).

Discussion

The incidence of stroke/TIA was the highest in women and non-Hispanic blacks in this cohort of PLWH followed regularly in ALLRT and its ACTG parent trials. In age-adjusted models, non-Hispanic blacks had a higher RR of stroke/TIA when compared with Hispanic and other race/ethnicities, although this effect no longer reached statistical significance in multivariable models. We also observed higher overall rates of stroke/TIA in women compared with men and found a significant interaction between age and sex on stroke/TIA risk. The increased RR of stroke/TIA in women was most pronounced in the 40–49-year age group and diminished with older age, whereas older age conferred a greater increase in stroke/TIA risk in men than women. Although we observed differences in age, race/ethnicity, and HIV RNA level between women and men, as well as several vascular risk factors at entry, the higher RR of stroke/TIA in women was still present after accounting for these factors in multivariable analyses.

Data from several large cohorts have suggested that vascular risk conferred by HIV may be greater in women than in men [1,2,6,7,13]. In the studies focused on cerebrovascular disease, absolute rates of stroke in women were still lower than in men [1,2], which is in line with the known epidemiology of stroke in the general population [14]. Our data are the first to suggest that women living with HIV may be at greater absolute risk of stroke/TIA compared with men. A similar finding of higher absolute rates of stroke in women with HIV has been presented from the Center for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort, with an age-standardized incidence of stroke among women of 5.02 compared with 2.88 per 1000 person-years in men [15], and should additionally be confirmed in other studies.

One proposed mechanism underlying observed sex differences in HIV-associated vascular risk is increased immune activation in women. Toll-like receptor 7 (TLR-7), which mediates innate immunity and activates monocytes, has been shown to promote greater levels of interferon-alpha in women with HIV compared with men, independent of the degree of viremia present [16]. Higher markers of monocyte activation have been detected in women with HIV, even after initiation of ART with successful virologic suppression, compared with men with HIV and men and women without HIV [17]. Moreover, the prevalence of noncalcified coronary plaque, a biomarker of cardiovascular risk, was higher in women with treated HIV and correlated with elevated monocyte activation, independent of traditional cardiovascular risk factors.

Declining estrogen levels in menopause, which affects immune activation and leads to a shift to a more proinflammatory state [18–20] may also modify the effect of HIV on vascular risk in women. In one study, reduced ovarian reserve contributed more to the burden of noncalcified coronary plaque among women with treated, virologically suppressed HIV than traditional vascular risk factors, whereas in uninfected women, the reverse was true [21]. One explanation of the observed age-by-sex interaction is that perimenopause may be a high-risk transition phase for women with HIV, leading to increased stroke rates. Then, as women reach postmenopause and more advanced age, female sex confers less of an increase in stroke risk among PLWH, while older age plays a greater role. Markers of immune activation and reliable data on menopause status and other women-specific stroke risk factors [22] (e.g. pregnancy, estrogen use) were not available in our study. A crucial next step will be to investigate how immune activation, menopause and other women-specific stroke risk factors, which can vary across the life course and thus may exert variable effects on stroke risk at different ages, interact, and influence stroke risk in women living with and without HIV.

Non-Hispanic blacks were also noted to have higher rates of stroke/TIA compared with individuals of Hispanic and other race/ethnicities and non-Hispanic whites, which is consistent with previously published studies of ischemic stroke risk in the general population, particularly in younger age groups [14,23,24]. This disparity is mediated, in part, by higher prevalence and worse control of traditional vascular factors among non-Hispanic blacks [25]. Indeed, we found that the higher RR of stroke/TIA among non-Hispanic blacks compared with non-Hispanic whites was no longer present after adjusting for various risk factors, including hypertension, elevated LDL, and smoking. However, the trend toward a higher RR of stroke/TIA for non-Hispanic blacks compared with Hispanics and other race/ethnicities after adjusting for traditional vascular and HIV-related risk factors raises the possibility that novel unmeasured factors may also be at play. Higher ischemic stroke risk for blacks has been noted in other observational cohort studies, including in the Veterans Aging Cohort Study-Virtual Cohort [5] and the Kaiser Permanente California database [4]. We also recently demonstrated in a group of ART-treated, virologically suppressed PLWH that blacks have worse cerebrovascular endothelial function compared with other race/ethnicities, independent of several traditional vascular risk factors [26]. Studies aimed at identifying mechanisms underlying vascular risk in HIV infection and developing novel strategies to reduce risk must have sufficient representation of non-white race/ethnicities and women in order to

understand disparities and to evaluate the efficacy of therapies in the highest risk groups.

Several traditional vascular risk factors, including hypertension and elevated LDL, were associated with a higher RR of stroke. Aggressive risk factor modification will be essential to stem the inevitable tide of stroke and other vascular complications as PLWH age [27]. In light of known discrepancies in risk factor control by race/ethnicity in the general population in the United States [28,29], particular attention to risk factor modification may be warranted in our patients of non-white race/ethnicity.

Of HIV-related risk factors associated with a higher risk of stroke/TIA, a nonsuppressed viral load conferred the greatest increase in stroke/TIA risk. Lower $CD4^+$ cell count was also a strong risk factor for stroke/TIA in age-adjusted and demographics-adjusted models but fell out of the multivariable model, likely because of collinearity with the presence of viremia. Importantly, we investigated whether the association of strokes with worse control of HIV infection may have been explained by strokes or misclassified strokes in the setting of common CNS opportunistic infections or malignancy. Of the 54 stroke/TIAs in the cohort, not one was associated with a recent diagnosis of a CNS infection or malignancy. The strong association of viral load and $CD4^+$ cell count with stroke/TIA generates the hypothesis that the immunologic sequelae of uncontrolled viremia may contribute to stroke risk in HIV infection. Although we did not have markers of immune activation for most of the individuals in the cohort, we found in age-adjusted and multivariable models that a higher $CD4^+$ to $CD8^+$ ratio was protective against stroke/TIA. The $CD4^+$ to $CD8^+$ ratio has been suggested as a proxy for immune activation and immunosenescence in HIV infection and is associated with an increased risk of several non-AIDS-related outcomes, including cerebrovascular events [30,31]. The strength of the association between lower $CD4^+$ to $CD8^+$ ratio and higher stroke/TIA risk was present even in a multivariable model adjusted for detectable viremia, suggesting that immune activation, which is a risk factor for stroke in the general population [32], may contribute to cerebrovascular risk in HIV infection independent of viral load.

One surprising finding was the protective effect that obesity had on stroke/TIA risk in the cohort. A similar effect of overweight/obese BMI on stroke risk in HIV infection was observed in the Kaiser Permanente California cohort [4]. Other studies have found a paradoxical association between higher BMI or plasma leptin, an adipokine directly correlated with fat cell mass, and lower cardiovascular risk [33–35]. The association between higher BMI and stroke risk could be confounded by overall health status, as individuals with higher BMI may be healthier and have better control of their HIV infection. However, the protective effect of higher BMI on stroke/TIA risk remained after adjustment for uncontrolled viremia. We also did not find a statistically significant interaction between BMI and age, sex, or smoking status to indicate that the protective effect of higher BMI was primarily in specific subgroups. As BMI does not account for body fat distribution, we also investigated markers of abdominal obesity. Neither greater waist-to-hip ratio nor greater waist circumference was associated with a significant decrease or increase in stroke/TIA risk in unadjusted or age-adjusted models. Although a provocative finding, the effect of overweight/obese BMI should be investigated in other cohorts before specific recommendations can be made regarding ideal BMI in PLWH.

Our study has several limitations. Although a physician reviewed data forms for the majority of reported stroke/TIAs, events were not formally adjudicated for this cohort. As a result, there may have been misclassification of outcomes, although this should not have been more or less likely based on sex or race/ethnicity. We also were not able to distinguish between ischemic and hemorrhagic stroke. Although prior data have demonstrated that HIV is an independent risk factor for both ischemic and hemorrhagic strokes [1,2], the pathophysiology underlying each differs and should ideally be studied separately. Differential loss-to-follow-up is always a potential source of bias in observational studies. In the ALLRT cohort, men were more likely to go off-study than women [36], although the implications on our findings of differential loss-to-follow-up by sex and other factors are unknown. In prior ALLRT analyses that have used statistical methods to correct for differential loss to follow up [37], findings were similar in adjusted and unadjusted analyses. Although model overfitting was a concern given the modest number of events, we felt reassured by the highly comparable results between the full multivariable models (Models 1 and 2) and both the demographic-adjusted models and the simplified multivariable model (Supplemental Table, http://links.lww.com/QAD/B244). However, our finding that women have higher absolute rates of stroke compared with men should be interpreted cautiously in light of the modest number of stroke events overall and in women.

In summary, in this large observational cohort of PLWH randomized to ART in one of several ACTG clinical trials, the highest incidence of stroke/TIA was among women and non-Hispanic blacks. Special attention should be paid to these at-risk populations as we design and implement studies focused on understanding and reducing elevated stroke risk in HIV infection. In addition to aggressively targeting modifiable vascular risk factors, efforts to engage and retain patients in care are paramount to addressing the role of uncontrolled viremia in stroke risk in HIV infection.

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Conflicts of interest

There are no conflicts of interest.

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