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Authors
Chow, Felicia C
Regan, Susan
Zanni, Markella V
et al.

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Elevated ischemic stroke risk among women living with HIV infection

Felicia C. Chow, MD, MAS[a], **Susan Regan, PhD**[b], **Markella V. Zanni, MD**[c], **Sara E. Looby, PhD**[c], **Cheryl D. Bushnell, MD**[d], **James B. Meigs, MD**[b], **Steven K. Grinspoon, MD**[c], **Steve K. Feske, MD**[e], and **Virginia A. Triant, MD, MPH**[b,f]

[a]Department of Neurology and Division of Infectious Diseases, University of California, San Francisco, CA

[b]Division of General Internal Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA

[c]Program in Nutritional Metabolism, Massachusetts General Hospital, Harvard Medical School, Boston, MA

[d]Department of Neurology, Wake Forest Baptist University Health Sciences, Winston-Salem, NC

[e]Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

[f]Division of Infectious Diseases, Massachusetts General Hospital, Harvard Medical School, Boston, MA

Abstract

Objective—To determine if the greater risk of ischemic stroke observed in women living with HIV infection (WLWH) compared with HIV-uninfected women persists after accounting for both traditional and sex-specific stroke risk factors.

Methods—We performed an observational cohort study of WLWH (n=1,214) and demographics-matched HIV-uninfected women (n=12,041) seen between 1996 and 2011 at two tertiary care hospitals in Boston. We used Cox proportional hazards regression analyses to model time to ischemic stroke, adjusting first for demographics and traditional stroke risk factors and then for sex-specific stroke risk factors, including menopause and estrogen use. We also constructed demographics-adjusted Cox models to identify HIV-related risk factors associated with ischemic stroke among WLWH.

Results—The incidence of ischemic stroke was higher among WLWH compared with HIV-uninfected women (incidence rate ratio 2.39, 95% CI 1.62–3.43). After adjusting for demographics and traditional stroke risk factors, HIV infection was associated with almost twice the risk of ischemic stroke (hazard ratio (HR) 1.93, 95% CI 1.31–2.85). The association of HIV with ischemic stroke persisted after inclusion of sex-specific stroke risk factors in the model (HR 1.89, 95% CI 1.28–2.81). Among WLWH, longer duration of antiretroviral therapy was associated with lower ischemic stroke risk (HR 0.86 per year, 95% CI 0.76–0.96).

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.

Conclusion—The increased risk of ischemic stroke among WLWH compared with HIV-uninfected women persisted after adjusting for both traditional and sex-specific stroke risk factors. Further investigation into the mechanisms of elevated stroke risk among WLWH, including immunologic factors, will be key for developing targeted preventive strategies for this at-risk population.

Introduction

Rates of ischemic stroke are higher in people living with HIV infection (PLWH)[1–3]. Female sex may play a unique role in the association between HIV infection and vascular disease. In the Partners HIV cohort, a large clinical care database of over 4000 PLWH and over 30,000 HIV-uninfected individuals, women living with HIV infection (WLWH) had nearly two times the adjusted hazard for ischemic stroke compared with uninfected individuals after accounting for traditional but not for sex-specific stroke risk factors[1]. Among men, however, there was no statistically significant difference in the risk of ischemic stroke by HIV status. A similar effect of female sex on myocardial risk has been observed in the Partners and other large cohorts[4–6]. Determining if the observed differential impact of sex on vascular risk in HIV infection persists after accounting for traditional and sex-specific risk factors is a first step toward understanding the mechanisms underlying these sex-based differences, informing future investigations into targeted sex-specific stroke risk reduction strategies for PLWH.

Recent American Heart Association/American Stroke Association guidelines dedicated to stroke risk prevention in women have garnered considerable attention, highlighting several stroke risk factors specific to or more prevalent in women, including menopause and pregnancy[7]. The role of these sex-specific stroke risk factors in mediating the association between HIV infection and ischemic stroke risk in women, while crucial to our understanding of sex-based differences in stroke risk, remains unclear. In this study, we expand upon the initial analyses in the Partners cohort by examining, for the first time in this cohort, the contribution of sex-specific risk factors to stroke risk in WLWH. In addition, whether HIV infection modifies the impact of sex-specific risk factors on vascular risk has, to our knowledge, never been investigated and may influence the relatively increased stroke risk in this unique population.

Our primary goal was to test the hypothesis that the relatively greater risk of ischemic stroke observed in WLWH in the Partners cohort persists after accounting for both traditional and sex-specific stroke risk factors. In addition, we aimed to identify HIV-related risk factors associated with ischemic stroke among WLWH.

Methods

Study design, setting and population

We conducted an observational cohort study of WLWH and HIV-uninfected women from the Partners HIV Cohort, a clinical care cohort derived from the Partners HealthCare System Research Patient Data Registry (RPDR). The RPDR is a clinical care database of all inpatient and outpatient data from Massachusetts General Hospital and Brigham and

Women's Hospital. We have previously evaluated rates of ischemic stroke in men and women from this cohort[1]. For the present study of women from the cohort, we included an additional 2 years of potential observation time. The start of the observation period was defined as the latest of: January 1, 1996; the date of first ICD-9-CM code for HIV; or the first encounter for the comparison cohort. Individuals were followed until the earliest of: occurrence of an ischemic stroke event; the date of the last encounter; or December 31, 2011. HIV infection was identified from the RPDR using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 042 or V08, which have been previously ascertained to be 99% sensitive and 89% specific for HIV infection in this cohort. We created a control group of HIV-uninfected women similar in age and race to the HIV cohort. This comparator group was generated by matching HIV-uninfected patients from the RPDR in a 10:1 ratio by demographics. The RPDR employs a matching algorithm that matches by sex and race, followed by age either by year or, if needed, by age group. Individuals 18 years and older at the beginning of the observation period with at least one inpatient or two outpatient clinical encounters were eligible for the study. The Partners Human Research Committee and University of California, San Francisco Committee on Human Research approved the study.

Study measurements

The outcome of interest was first-ever ischemic stroke, defined by either one inpatient or two outpatient ICD-9-CM codes of 433.xx, 434.xx (excluding codes with a 0 as the 5^{th} digit), 437.0, 437.4, 437.5, 443.21 or 443.24. Codes were selected to align with the stroke definition employed in our prior study evaluating rates of ischemic stroke in men and women from this cohort. Individuals with ICD-9-CM codes for ischemic stroke prior to the first ICD-9-CM code for HIV or to the start of the observation period were excluded. We obtained data on traditional stroke risk factors during the observation period using ICD-9-CM codes, including hypertension (401.xx), diabetes mellitus (250.xx), atrial fibrillation (427.3), coronary heart disease/myocardial infarction (CHD/MI, 410.xx, 411.xx, 412.xx, 414.xx), and chronic kidney disease (CKD, 585.x, 403.xx, 404.xx). Validation of several of these diagnoses through medical record review, including for hypertension, diabetes, and CHD/MI, has been performed in this cohort[8]. Smoking status was determined through a natural language processing-based algorithm that assigns smoking status by scanning electronic medical record text, identifying smoking-related information, classifying the text as indicating a current smoker, former smoker, or non-smoker, and integrating all available text for each patient into a smoking status (ever/never or current/not current in a calendar year).[9] Patients with no smoking-related documentation in the medical record were considered non-smokers. We also obtained medication data on use of statins, antiplatelet agents, and oral anticoagulation during the observation period. We determined HIV parameters, including duration of combination antiretroviral therapy (ART) use, most recent CD4 count and HIV viral load before the end of the observation period, and nadir CD4 count, for the HIV cohort.

Based on the median age of menopause in a multi-ethnic cohort of women in the U.S.[10], we defined menopause as a composite variable of 1) age 51 years or older at the beginning of the observation period or 2) at least one ICD-9-CM code for menopause-associated

symptoms and conditions [e.g.. premature menopause/ovarian failure (256.31), menopausal and postmenopausal disorders (627.x), asymptomatic postmenopausal status (V49.81)] regardless of age. We obtained data on a history of post-surgical menopause (256.2) or prior hysterectomy with or without oophorectomy, defined by current procedural terminology (CPT) codes, during the observation period. Inpatient and outpatient medication lists were used to determine any estrogen use, although we were unable to reliably distinguish between estrogen use for oral contraception and hormone replacement therapy. Additionally, we extracted data using ICD-9-CM codes for diagnoses or conditions during the observation period specific to women [e.g., history of pregnancy, pre-eclampsia or eclampsia (642.4-7x), polycystic ovary syndrome (256.4)] and for diagnoses more common among women [e.g., hypercoagulable state (289.81, 289.82), migraines (346.0-9x), depression (296.2x, 296.3x, 300.4, 311, 293.83) and/or anxiety (300.00–300.03, 300.09, 300.2x, 309.24, 293.84)].

Statistical analysis

We determined the overall and age-stratified incidence rates of ischemic stroke per 1,000 person-years (PY) of follow-up time in the HIV and HIV-uninfected cohorts. For each age group, we calculated the incidence rate ratio comparing WLWH with uninfected women, in addition to the absolute difference in rates of ischemic stroke by HIV status. We used Cox proportional hazards regression analyses to model the time to incident ischemic stroke, adjusting for age, race, and traditional ischemic stroke risk factors. We then added sex-specific stroke risk factors to the model to evaluate their influence on the association between HIV infection and the hazard of ischemic stroke. Because no women with a history of hysterectomy or polycystic ovary syndrome had an ischemic stroke event, both variables were dropped from the multivariable analysis. We tested for the presence of statistical interactions between HIV and several sex-specific stroke risk factors, including menopause, estrogen use and pregnancy by adding each interaction term individually to the final multivariable model adjusted for age, race, traditional and sex-specific stroke risk factors. We also constructed Cox proportional hazards models restricted to WLWH to assess factors associated with ischemic stroke. For these models, because of the relatively modest number of events in WLWH, we estimated the association between each individual variable of interest and the hazard of ischemic stroke in models adjusted only for age and race. All p values were 2-sided with $p \leq 0.05$ considered statistically significant.

Results

Demographics and clinical characteristics

The cohort consisted of 13,255 women, of whom 1,214 were living with HIV infection. The women contributed a total of 98,370 PY of observation time. The median length of follow-up for both WLWH and for HIV-uninfected women was 7 years. The mean age of WLWH at the start of the observation period was 40 years and of uninfected women was 39 years. The race/ethnicity distribution for WLWH and HIV-uninfected women, respectively, were 39% and 41% white, 33% and 31% black, and 19% and 18% Hispanic. Among those who had had an HIV RNA viral load, 61% were virologically suppressed. The median HIV RNA was undetectable, which we designated as 1 copy/ml for the log transformation to equal 0 log copies/ml. The prevalence of most traditional stroke risk factors, including hypertension,

diabetes mellitus, and smoking, was higher among WLWH compared with uninfected women (Table 1). There was no statistically significant difference in the proportion of women using statins, antiplatelet medications or oral anticoagulants by HIV status. Several of the sex-specific stroke risk factors were also more common among WLWH, including menopausal status, use of estrogen, prior hysterectomy, hypercoagulability, migraines and depression/anxiety (Table 1).

Incidence rates of ischemic stroke

One hundred ninety-six ischemic strokes occurred over 98,370 PY, resulting in an ischemic stroke incidence rate of 1.99 per 1000 PY, with 37 events in the HIV cohort and 159 in the uninfected cohort. The incidence rate for WLWH was 4.24 per 1000 PY compared with 1.77 per 1000 PY in the uninfected cohort, resulting in an overall incidence rate ratio of 2.39 (95% confidence interval (CI) 1.62–3.43) (Table 2). The incidence rate of ischemic stroke was higher among WLWH compared with uninfected women in all age strata, although the relative increase in the rate associated with HIV infection was more pronounced and reached statistical significance only in younger age groups (Table 2, Figure 1). We also calculated the absolute difference in incidence rates between WLWH and uninfected women, which was similar among age groups up to 65 years of age, with an additional 2.15 to 2.59 events per 1000 PY in the HIV cohort (Table 2).

Association of HIV infection and ischemic stroke

In an unadjusted model, HIV infection was associated with a nearly 2.5-fold higher hazard of ischemic stroke (Figure 2). In a multivariable model, adjusted for age, race, hypertension, dyslipidemia, diabetes mellitus, CKD, CHD/MI, atrial fibrillation, structural heart disease, endocarditis, smoking, antiplatelet/anticoagulant and statin use, the association between HIV and ischemic stroke was attenuated, although HIV was still associated with nearly twice the hazard of ischemic stroke (HR 1.93, 95% CI 1.31–2.85). The addition of sex-specific stroke risk factors (menopause status, estrogen use, history of pregnancy, pre-eclampsia/eclampsia, hypercoagulable disorder, migraines, and depression/anxiety) to the multivariable model did not substantially impact the association of HIV with ischemic stroke (HR 1.89, 95% CI 1.28–2.81) (Figure 2). Other risk factors for ischemic stroke in the adjusted model for the entire cohort of infected and uninfected women included: older age, structural heart disease, smoking, and a composite variable of antiplatelet/anticoagulant use (see Supplemental Table). There was a trend toward a higher hazard of ischemic stroke associated with hypertension, CHD/MI and endocarditis but confidence intervals were too wide to rule out no association.

Risk factors for ischemic stroke among WLWH

In age- and race-adjusted exploratory models restricted to WLWH, longer duration of ART use was protective against ischemic stroke (HR 0.86 per year of ART use, 95% CI 0.76–0.96), while a history of a CNS opportunistic infection or malignancy was associated with a higher hazard of ischemic stroke (HR 2.87, 95% CI 1.00–8.23) (Table 3). Estrogen use was associated with a trend toward a decreased risk of ischemic stroke (Table 3). We did not find a statistically significant association between any of the other HIV-related risk factors, including nadir CD4 count, most recent CD4 count or HIV RNA level, and ischemic stroke.

Interaction between HIV and sex-specific stroke risk factors on ischemic stroke risk

To investigate whether any sex-specific risk factors differentially impacted ischemic stroke risk by HIV status, we performed sensitivity analyses to evaluate for differences in the association of these risk factors, including menopause, estrogen use, and pregnancy, in WLWH compared with uninfected women by adding interaction terms for HIV with each sex-specific variable individually to the full multivariable model adjusted for age, race, traditional and sex-specific stroke risk factors. None of these interaction terms was statistically significant.

Discussion

In this large cohort of WLWH and HIV-uninfected women, we demonstrated that HIV infection is an independent risk factor for ischemic stroke after accounting for both traditional and sex-specific stroke risk factors. While sex-specific risk factors may indirectly mediate the association between HIV infection and ischemic stroke risk through traditional stroke risk factors (i.e., post-menopausal women have higher rates of traditional stroke risk factors), we did not find evidence that sex-specific stroke risk factors further mediate this association after accounting for traditional risk factors. These results suggest that novel, HIV-related factors that remain unaccounted for may be relevant to ischemic stroke risk among WLWH.

In this and other large cohorts, the relative risk associated with HIV infection for several vascular outcomes, including myocardial infarction and both ischemic and hemorrhagic stroke, has been greater in women than in men[1,4–6,11]. Sex-based variability in immune mechanisms may drive the increased relative risk of ischemic stroke in WLWH. In general, women mount more robust immunologic responses to infections compared with men.[12] Greater interferon-alpha production by plasmacytoid dendritic cells triggered by Toll-like receptor 7 (TLR7) has been documented in women compared with men,[13] including in response to HIV infection.[14] Although this heightened immune response can translate into more effective virologic control,[15] the associated inflammation may impact the development of non-AIDS-related comorbid conditions, including stroke. In one study of predominantly virologically suppressed PLWH, WLWH had higher levels of monocyte activation markers (e.g., soluble CD163) than men living with HIV, which correlated with a greater burden of non-calcified coronary plaque, independent of traditional cardiovascular risk factors[16].

Age-related changes in monocyte activation may also occur at a faster rate in WLWH compared with uninfected women[17] and may be more pronounced in women compared with men living with HIV.[16] Among WLWH, exacerbation of the augmented, age-related immune activation that occurs in HIV infection[18] may be propelled by estrogen depletion in the peri- and postmenopausal periods.[19,20] Estrogens generally inhibit monocyte and macrophage activity,[21] leading to suppression of proinflammatory pathways and lower levels of IL-6 and other cytokines strongly associated with cardiovascular outcomes, including stroke, in HIV.[22–24] In a clinical trial of postmenopausal women, administration of 17β-estradiol augmented TLR7-stimulated interferon production, while inhibition of estrogen receptor signaling resulted in the opposite effect.[25,26] As estrogen levels decline

during the peri-menopause transition, a simultaneous rise in inflammatory cytokines ensues, [19,20] which could precipitate cerebrovascular risk in WLWH. The effect of age and hormone-related alterations in monocyte activation on cerebrovascular risk may be further hastened or modified by HIV infection. In one study, the impact of reduced ovarian reserve, measured by anti-Mullerian hormone levels, on non-calcified coronary plaque burden among WLWH was greater than the contribution of traditional cardiovascular risk factors, whereas in uninfected women, the reverse was true[27].

In a recent study from the AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) cohort, WLWH had a higher absolute rate of stroke compared with men living with HIV infection.[28] The effect of female sex on stroke rates in the ALLRT cohort was modified by age, with women in the 40 to 49 year age group having the greatest increase in stroke risk compared with men. This finding raises the possibility that the peri-menopausal transition could be a vulnerable period for WLWH in terms of stroke risk. In the general population, earlier age at menopause has been associated with increased ischemic stroke risk.[29–31] WLWH may undergo menopause earlier[32] and have lower serum estradiol levels independent of age compared with uninfected women.[33] While menopause was not a risk factor for ischemic stroke in this study, our definition did not allow us to precisely capture the menopause transition, which may be a more clinically relevant time period than post-menopause. We did observe a trend toward a protective effect of estrogen use against ischemic stroke among WLWH. While there is ongoing uncertainty regarding the net cardiovascular benefit and impact of timing of exposure and route of administration of menopausal hormone therapy in the general population,[34–36] further investigation into the impact of estrogen depletion and replacement across the menopause transition in WLWH is warranted.

As expected, rates of ischemic stroke increased with older age regardless of HIV status (Figure 1). The relative increase in stroke risk among WLWH compared with uninfected women, however, was greatest in younger age strata. WLWH between the ages of 18 and 35 years had over 5-fold higher hazard of ischemic stroke compared with uninfected women, while WLWH older than 65 years did not have a statistically significantly higher hazard of stroke compared with their uninfected counterparts. Rate ratios, however, can be misleading when the reference rate of the outcome of interest in the comparator group is low, as is the case for younger women. A modest absolute increase in the ischemic stroke rate in WLWH could easily result in a doubling or tripling of the low reference rate in uninfected women. On the other hand, when the reference rate in the comparator group is higher as with older women, a much larger absolute increase in stroke rates must occur before achieving a two or three-fold increase. To account for this potential effect, we also calculated the absolute incidence rate difference by HIV status and found it to be relatively uniform across age groups, ranging from 2 to 2.5 additional ischemic stroke events per 1000 PY in WLWH compared with uninfected women in all age groups except the oldest. Although age-stratified event rates were too low to draw a strong conclusion, the relatively stable absolute incidence rate difference across age groups argues against an interaction between age and HIV on ischemic stroke risk in women.

We found a strong and statistically significant association between duration of ART use and lower risk of ischemic stroke. This finding mirrors our prior study of men and women from this same cohort, along with other studies, which demonstrated ART use and duration to be protective against ischemic stroke.[1,37] Longer duration of ART use may be a proxy for degree of immunodeficiency, although we did not observe an association between lower current or nadir CD4 count and greater risk of ischemic stroke. In other cohort studies, immunodeficiency and uncontrolled viremia have been linked with increased cerebrovascular risk,[2,3,38,39] including in the Partners cohort when we included a larger group of men and women.[1] In one study of over 2,000 women from the Veterans Aging Cohort, of which nearly one-third were HIV-infected, WLWH had a significantly increased risk of a composite outcome of cardiovascular disease, including ischemic stroke, regardless of baseline CD4 count. A stepwise increase in the hazard ratio for cardiovascular disease (comparing WLWH with uninfected women) with decreasing CD4 count was observed, although differences in risk by CD4 count did not reach statistical significance.[40] One possible explanation for the lack of an association of CD4 count and viral load with ischemic stroke risk in the present study is that we were underpowered to detect a significant association due to the relatively low number of ischemic stroke events in WLWH. Another hypothesis is that the influence of immunodeficiency or uncontrolled viremia on ischemic stroke risk among WLWH may be different than in men living with HIV, who have comprised the vast majority of studies that have observed a significant effect of CD4 count or viral load on vascular risk.

Our findings should be interpreted alongside the limitations of the study. Although the HIV-infected cohort and HIV-uninfected comparator group are derived from the same health care system and are generally from a similar geographic region, we had limited data on health-related behaviors, including substance use, and socioeconomic factors, which, if disproportionately present among vulnerable WLWH, could have resulted in higher stroke rates in HIV infection. Similarly, although the median observation time between the 2 groups was comparable, less frequent monitoring among HIV-uninfected women for comorbid conditions during the follow-up period could have led to an erroneously low prevalence of vascular and sex-specific risk factors. In addition, use of ICD-9-CM codes to define predictors and outcomes in the cohort may have insufficiently captured several variables of interest, including sex-specific stroke risk factors. Menopause, in particular, is challenging to define in clinical databases that rely on electronic medical record data and administrative billing codes. In fact, even medical record review to ascertain menopause status may be inadequate as, for many women, menopause is not a condition requiring medical attention. Menopause was a risk factor for ischemic stroke in an unadjusted model (Supplemental Table), which likely reflects the age component of the definition. The protective effect of menopause against ischemic stroke in both the overall cohort and in WLWH after adjustment for age may point to the benefit of greater engagement in and access to care of women who actually sought attention for menopausal and postmenopausal disorders. While the cohort studied was large and developed to assess mediators of the association of HIV with stroke in a combined HIV and non-HIV cohort, the modest number of ischemic stroke events in the group of HIV-infected women precluded us from constructing a multivariable model to understand the influence of several factors, including

potential confounding and effect modification, on ischemic stroke risk in WLWH. The modest number of ischemic stroke events in the HIV-infected cohort could explain the lack of a significant association between certain well-established vascular risk factors (e.g., hypertension, atrial fibrillation) and stroke events among WLWH. Furthermore, we could not discern the indication for estrogen use in the cohort (i.e., oral contraception versus hormone replacement therapy), which constrained our ability to identify a possible differential impact on stroke risk. Finally, as with any non-randomized observational study, our results may have been affected by unmeasured or residual confounding. For example, we lacked reliable data on substance use, which could explain higher rates of ischemic stroke in WLWH, especially in younger age groups. Notably, the ALLRT cohort has few intravenous drug users and, even after accounting for drug use, the higher rate of stroke among WLWH was still present.

In summary, the increased risk of ischemic stroke among WLWH compared with uninfected women persisted after adjusting for both traditional and sex-specific stroke risk factors. With women constituting more than half of the world's HIV population, ongoing investigation into potential risk factors for stroke among WLWH, including the role of immune activation and inflammation as well as more precise measures of estrogen depletion across the menopause transition is imperative and will facilitate the development of tailored prevention strategies for this group.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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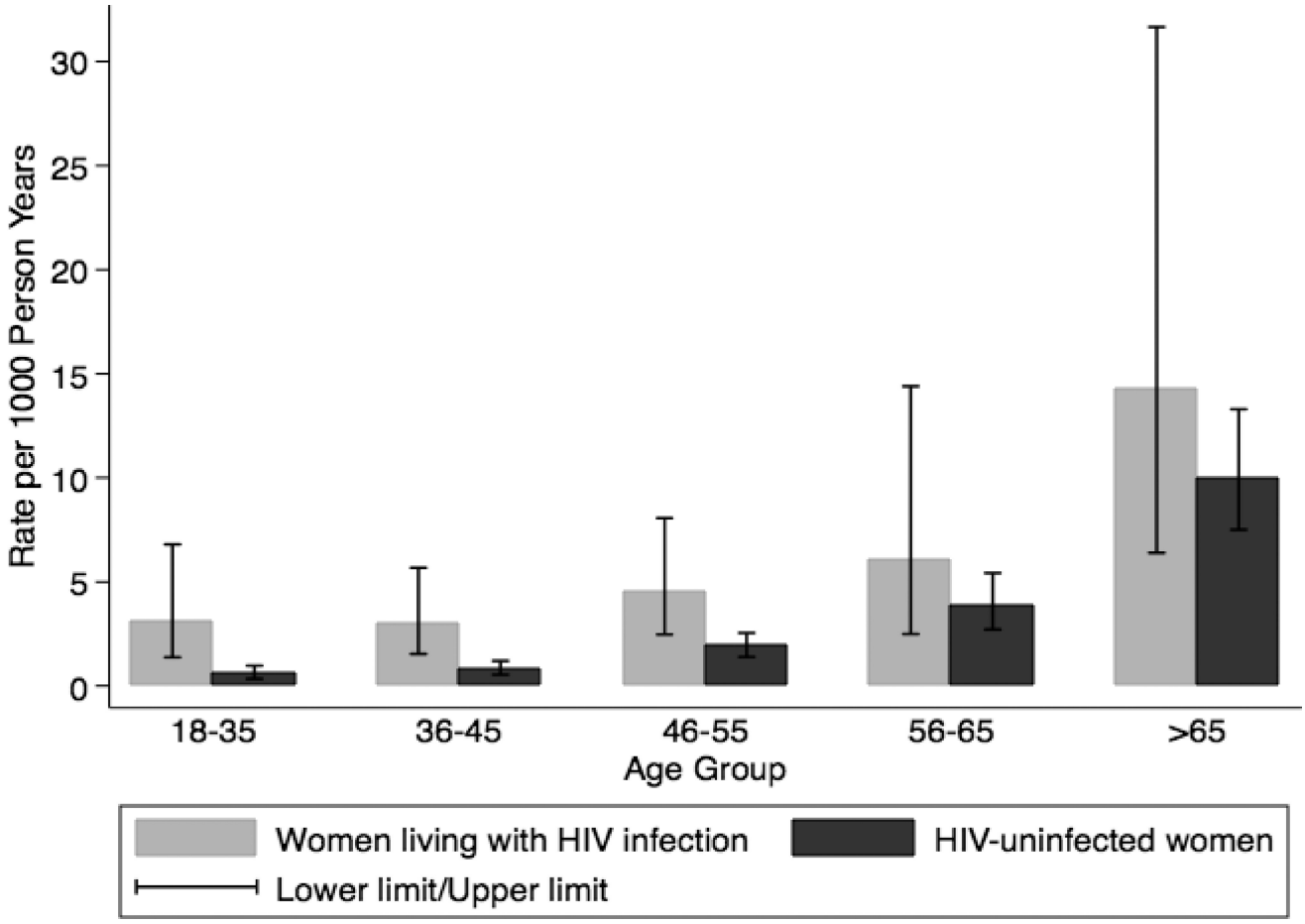

Figure 1. Incidence rates for ischemic stroke in the Partners HIV cohort stratified by HIV status and age

Incidence rates were higher overall in women living with HIV infection (WLWH) compared with HIV-uninfected women. The relative increase in stroke rates for WLWH was present in all age groups but only statistically significant among younger women (<55 years).

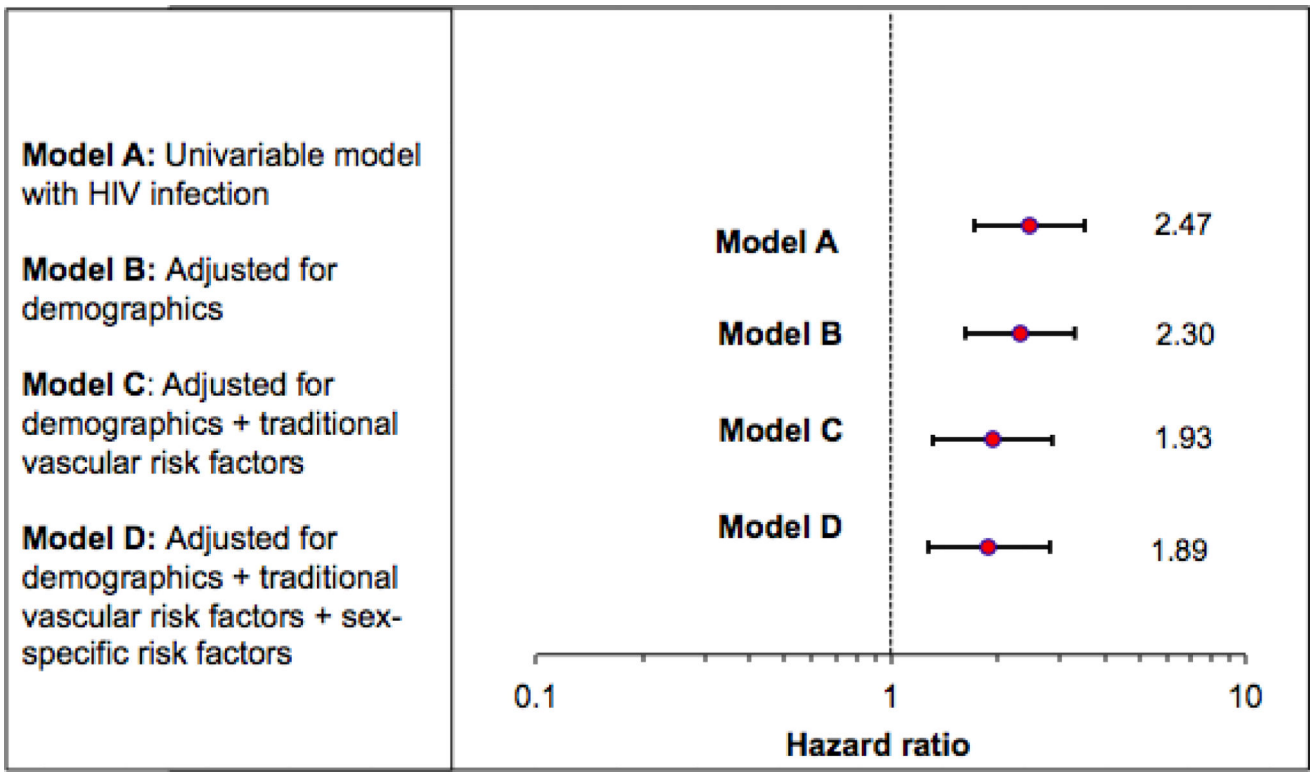

Figure 2. Hazard ratio for ischemic stroke associated with HIV infection in women from the Partners HIV cohort

After adjustment for age, race, traditional vascular risk factors (hypertension, dyslipidemia, diabetes mellitus, coronary heart disease, chronic kidney disease, atrial fibrillation/flutter, endocarditis, structural heart disease, smoking, statin and antiplatelet use), and sex-specific risk factors (menopause, estrogen use, pregnancy, eclampsia, migraines, depression), HIV infection was still associated with nearly twice the hazard of ischemic stroke.

Table 1

Demographic and clinical characteristics of a cohort of women living with HIV infection (WLWH) and HIV-uninfected women from the Partners HIV cohort

	WLWH (n=1214)	HIV-uninfected (n=12,041)	P value
Demographics (% of total unless noted)			
Age (years), mean (SD)	40 (12)	39 (13)	0.003
Race/ethnicity			
-White	39	41	
-Black	33	31	
-Hispanic	19	18	0.44
-Other	4	3	
-Unknown	6	6	
Vascular and other risk factors (% of total unless noted)			
Hypertension	37	24	<0.001
Dyslipidemia	39	22	<0.001
Diabetes mellitus	22	10	<0.001
Chronic kidney disease	11	2	<0.001
Coronary heart disease	17	7	<0.001
Atrial fibrillation/flutter	3	2	0.002
Structural heart disease	19	8	<0.001
Endocarditis	4	1	<0.001
Statin use	11	11	0.92
Antiplatelet/anticoagulation use	14	13	0.37
Ever smoker	52	37	<0.001
Sex-specific risk factors (% of total unless noted)			
Menopausal	30	27	0.029
Estrogen use	15	12	0.006
Prior hysterectomy	1	<1	0.001
Prior pregnancy	27	28	0.50
Pre-eclampsia/eclampsia	3	2	0.15
Polycystic ovary syndrome	1	1	0.40

	WLWH (n=1214)	HIV-uninfected (n=12,041)	P value
Hypercoagulable state	1	<1	0.001
Migraines	14	10	<0.001
Depression or anxiety	31	17	<0.001
HIV-related risk factors (% of total unless noted)			
CD4 count * (cells/mm^3), mean (SD)	543 (369)	---	---
Nadir CD4 (cells/mm^3), mean (SD)	263 (276)	---	---
HIV RNA * (log, copies/ml), median (IQR)	0 (0, 2.84)	---	---
Duration of antiretroviral therapy (years), median (IQR)	6 (3, 10)	---	---
CNS opportunistic infections/malignancy	4	<1	<0.001

Abbreviations: SD, standard deviation; CNS, central nervous system

* Most recent values before the end of the observation period

Table 2

Incidence rates for ischemic stroke in the Partners HIV cohort stratified by HIV status and age

Incidence rates were higher overall in women living with HIV infection (WLWH) compared with HIV-uninfected women. The relative increase in stroke rates for WLWH was present in all age groups but only statistically significant among younger women (<55 years).

	All women		HIV-infected		HIV-uninfected		Incidence rate ratio	Incidence rate difference
Age Group	Events	Rate	Events	Rate	Events	Rate	IRR (95% CI)	Rate difference
18–35	20	0.76	6	3.05	14	0.57	5.31 (1.67–14.72)	2.48 (0.02–4.94)
36–45	33	1.00	9	2.95	24	0.80	3.68 (1.50–8.20)	2.15 (0.19–4.11)
46–55	53	2.14	11	4.47	42	1.88	2.37 (1.10–4.69)	2.59 (−0.11–5.29)
56–65	37	4.03	5	5.99	32	3.83	1.56 (0.48–4.04)	2.16 (−3.26–7.58)
>65	53	10.34	6	14.23	47	9.99	1.42 (0.50–3.34)	4.24 (−7.50–15.97)
Total	**196**	**1.99**	**37**	**4.24**	**159**	**1.77**	**2.39 (1.62–3.43)**	**2.46 (1.07–3.86)**

*All rates per 1000 PY

Table 3

Risk factors associated with ischemic stroke among women living with HIV infection (WLWH) from the Partners HIV cohort in unadjusted and age and race-adjusted models

	Unadjusted model		Age and race–adjusted model	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age (per 10 years)	1.55 (1.26–1.90)	<0.001	---	---
White race	1.11 (0.58–2.14)	0.75	---	---
Hypertension	1.76 (0.92–3.39)	0.089	1.15 (0.56–2.34)	0.71
Diabetes mellitus	1.11 (0.54–2.30)	0.78	0.95 (0.45–1.97)	0.88
Chronic kidney disease	2.32 (1.09–4.92)	0.029	1.66 (0.76–3.64)	0.20
Coronary heart disease	2.93 (1.52–5.65)	0.001	2.15 (1.08–4.30)	0.030
Atrial fibrillation	3.82 (1.35–10.80)	0.011	2.01 (0.65–6.22)	0.23
Endocarditis	1.98 (0.61–6.45)	0.26	1.83 (0.56–5.97)	0.32
Structural heart disease	3.57 (1.87–6.82)	<0.001	2.83 (1.44–5.56)	0.003
Smoker	1.32 (0.68–2.58)	0.41	1.35 (0.69–2.63)	0.39
Statin use	0.53 (0.16–1.74)	0.30	0.40 (0.12–1.33)	0.14
Antiplatelet and/or anticoagulant use	0.79 (0.31–2.03)	0.62	0.64 (0.25–1.65)	0.35
Menopause	1.20 (0.62–2.35)	0.59	0.36 (0.14–0.93)	0.035
Estrogen use	0.14 (0.02–1.03)	0.054	0.18 (0.02–1.29)	0.088
Pregnancy	0.40 (0.16–1.03)	0.058	0.67 (0.25–1.84)	0.44
Hypercoagulable	3.09 (0.42–22.55)	0.27	2.12 (0.28–15.92)	0.46
Migraine	0.79 (0.31–2.04)	0.63	0.92 (0.36–2.37)	0.86
Depression	1.08 (0.55–2.10)	0.83	1.12 (0.57–2.19)	0.74
Duration of ART	0.83 (0.74–0.94)	0.002	0.86 (0.76–0.96)	0.008
CD4 count (per 50 cells/mm^3) *	1.00 (0.94–1.06)	0.93	1.00 (0.94–1.05)	0.91
Nadir CD4 count (per 50 cells/mm^3)	1.01 (0.94–1.09)	0.75	1.01 (0.94–1.09)	0.76
HIV RNA (per 1 log copy/mL) *	1.13 (0.85–1.51)	0.39	1.11 (0.83–1.48)	0.48
CNS infections/malignancy	2.39 (0.84–6.78)	0.10	2.87 (1.00–8.23)	0.050

Abbreviations: ART, antiretroviral therapy; CNS, central nervous system

* Most recent values before the end of the observation period