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Factors associated with worse cerebrovascular function in aging women with and at risk for HIV

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Abstract

Objective—Women may be disproportionately impacted by the negative effect of HIV on cerebrovascular risk. We examined the association of HIV, sex, menopause, and immune activation with cerebrovascular function among women with HIV (WWH) and at risk for HIV from the Women's Interagency HIV Study and men with HIV (MWH).

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Conflicts of interest

The authors report no conflicts of interest relevant to this study. PYH reports receiving honoraria from Merck and Gilead unrelated to this study.

Design—Cross-sectional

Methods—Participants were aged ≥40 years with coronary heart disease or at least one cardiometabolic risk factor. All persons with HIV were on antiretroviral therapy with undetectable viral load. Cerebral vasoreactivity was assessed by the transcranial Doppler breath-holding test, with lower vasoreactivity corresponding to worse cerebrovascular function. Menopausal status was determined by anti-Mullerian hormone level. We used mixed effects linear regression to identify factors associated with cerebral vasoreactivity.

Results—Mean cerebral vasoreactivity was similar in WWH (n=33) and women at risk for HIV (n=16). A trend toward higher cerebral vasoreactivity in WWH compared with MWH (n=37) was no longer present after excluding women on estrogen replacement therapy (n=3). In women, menopausal status was not significantly associated with cerebral vasoreactivity. WWH with higher cardiovascular risk (−0.14 for each additional cardiometabolic risk factor, p=0.038), sCD163 (−0.20 per doubling, p=0.033), and proportion of CD4+CX3CR1+ T cells (−0.14 per doubling, p=0.028) had lower cerebral vasoreactivity.

Conclusion—Among older women at high cardiovascular risk, women with virologically suppressed HIV and women at risk for HIV had similar cerebrovascular function. Our findings, which must be interpreted in the context of the small sample, highlight the contribution of traditional cardiometabolic risk factors and immune activation to cerebrovascular risk in WWH.

Keywords

Cerebrovascular function; cerebral vasoreactivity; stroke; cardiovascular risk; women; HIV

Stroke rates are higher in persons with HIV (PWH) than in individuals without HIV[1–5]. An unexpected observation that has been corroborated in at least two large prospective cohorts is that women with HIV (WWH) may have higher absolute rates of stroke compared with men with HIV (MWH)[6,7]. Furthermore, the increased risk of stroke conferred by HIV infection may be greater for women than for men[8]. In the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials cohort, the incidence of stroke in WWH was 2.88 per 1000 person-years compared with 1.40 per 1000 person-years for MWH[6]. Even after accounting for demographics, cardiometabolic risk factors, and HIV-related variables, the relative risk of stroke for a woman compared with a man at age 50 was 1.94 (95% CI 1.03–3.66). A statistically significant age-by-sex interaction was observed, with women age 40 to 49 years having the greatest relative risk compared with men of the same age. Although the mechanisms underlying the increased risk of stroke observed in WWH in this age group are unknown, one hypothesis is that the perimenopausal transition may be a time of particularly high stroke risk for WWH.

We previously found that cerebral vasoreactivity, a measure of cerebrovascular endothelial function[9] associated with cerebral small vessel disease and large artery atherosclerosis[10–12], is reduced in PWH with well-controlled infection compared with individuals without HIV[13,14]. However, these studies assessed cerebral vasoreactivity in cohorts with few to no women. Studies in the general population suggest cerebral vasoreactivity may decline as women transition through menopause, whereas a decline with older age has not been consistently observed in men[15,16]. In addition, fluctuations in cerebral vasoreactivity

during the menstrual cycle provide evidence that sex hormones directly impact cerebrovascular function[17]. For WWH, the observed higher risk of stroke may be due to the combined effects of HIV with estrogen depletion on cerebrovascular function.

To examine the association of HIV, sex, and other risk factors with cerebrovascular function and ischemic stroke risk, we compared cerebral vasoreactivity among older WWH and women at risk for HIV from the Women's Interagency HIV Study (WIHS) and MWH, all with a history of coronary heart disease (CHD) or of at least one cardiometabolic risk factor. We hypothesized that menopause would have a greater negative impact on cerebrovascular dysfunction in WWH and that WWH would have lower cerebral vasoreactivity compared with men.

Methods

Study population

WIHS was established in 1993 as an ongoing, prospective study of the progression of HIV in women with and at risk for HIV. From 1994 to 2015, WIHS enrolled 4982 women (3,678 WWH and 1,304 women at risk for HIV) during four recruitment waves from 10 sites (Bronx and Brooklyn, NY; Chicago, IL; San Francisco, CA; Los Angeles, CA; Washington D.C.; Atlanta, GA; Chapel Hill, NC; Miami, FL; Jackson, MS; and Birmingham, AL). At semi-annual visits, participants completed a physical examination, provided biological specimens, and completed an interviewer-administered questionnaire. All eligible women from the San Francisco Bay Area WIHS site (SF WIHS) were invited to participate in this sub-study.

To evaluate the effect of sex on cerebral vasoreactivity, we included data from a cohort of MWH recruited from the Study on the Consequences of the Protease Era (SCOPE) who underwent transcranial Doppler ultrasound (TCD) as part of a neurologic sub-study of a randomized clinical trial. All data on cardiometabolic risk factors, health-related behaviors, and HIV-associated variables were collected from the most recent visit before the TCD prior to randomization and assignment to intervention.

All participants had to be ≥40 years of age with a history of CHD or of at least one cardiometabolic risk factor (e.g., diabetes mellitus, hypertension, dyslipidemia, current smoker). PWH had to be on antiretroviral therapy (ART) for at least 1 year with an HIV RNA below the standard limit of quantification for at least 6 months and CD4 cell count ≥400 cells/mm^3. Written informed consent was obtained from all participants.

Outcome

To evaluate cerebrovascular function, we assessed cerebral vasoreactivity of the bilateral middle cerebral arteries in response to a breath-holding challenge[18], which has been shown to have good short and long-term reproducibility[18–20]. The primary outcome for cerebral vasoreactivity was the breath-holding index (BHI), defined as the percent change in mean flow velocities measured with TCD from baseline to the conclusion of breath-holding per second. A lower BHI correlates with worse cerebrovascular function. Normal BHI values for adults 30 to 69 years range from 1.27 to 1.44 with a standard deviation (SD) of

approximately 0.30[21]. A single vascular technologist blinded to HIV status performed all studies. Results from 2 consecutive trials were averaged. Pre-menopausal women were studied in the first week of their menstrual cycle to account for the effect of estrogen on vasoreactivity.

Covariates

Demographics, cardiometabolic risk factors, estrogen use, health-related behaviors, HIV-associated variables, and laboratory data from the most recent visit prior to the TCD study were included in the analysis. Hypertension was defined as: 1) report of anti-hypertensive medication use, 2) report of hypertension, or 3) systolic blood pressure ≥140 or diastolic blood pressure ≥90 at any prior visit. Diabetes mellitus (DM) was defined as: 1) report of anti-DM medication use, 2) report of DM confirmed by two fasting glucose (FG) measurements ≥126mg/dL or FG ≥126mg/dL with hemoglobin A1C (A1C) ≥6.5%, or 3) FG ≥126mg/dL confirmed by subsequent FG ≥126mg/dL or A1C ≥6.5%. A history of CHD, stroke, smoking and alcohol use were collected via self-report. Waist circumference and body mass index were measured at the WIHS visit.

We created a cardiovascular risk score that reflected the combined number of cardiometabolic risk factors (CHD, DM, hypertension, dyslipidemia, current smoker) per participant, ranging from 1 to 5 total risk factors. Hepatitis C virus (HCV) infection was defined as a positive HCV antibody test with detectable HCV RNA.

Menopausal status

Anti-Mullerian Hormone (AMH), a marker of ovarian reserve, was tested serially from unthawed plasma samples frozen at −80°C using the Beckman Gen II AMH enzyme-linked immunosorbent assay (ELISA) (Beckman Coulter Inc, MN USA) and, starting in March 2017, the Beckman Automated DxI AMH ELISA. The Beckman AMH ELISA lower limit of detection is 0.08 ng/mL. Samples were run in duplicate for the Beckman Gen II manual ELISA with inter- and intra-assay coefficients of variation <15%. Samples were run in singlicate for the automated ELISA with inter-assay coefficient of variation <7.4%. We calibrated older AMH values to the new values[22], as values from the automated ELISA tended to read lower than the manual ELISA. In women with undetectable AMH (<0.08 ng/mL) at their most recent visit, serial measurements were performed every one to two years retrospectively until the last detectable AMH timepoint was identified. The first undetectable AMH was defined as entry into late perimenopause, which per the STRAW+10 criteria occurs 1 to 3 years before the final menstrual period (FMP)[23,24]. A recent study found that the probability of reaching the FMP within 36 months at a given AMH threshold increased with age[25]. For women <48 years with AMH between 0.05 and 0.10 ng/mL, the probability of reaching the FMP within 36 months was 39% compared with 69% for women 48 to 51 years and 71% for women >51 years. Using an ultrasensitive AMH assay with levels of detection <0.01 ng/mL, AMH between 0.01 and <0.025 ng/mL increased the probability of reaching the FMP to 71% for women <48 years, 87% for women 48 to 51 years, and 90% for women >51 years. We used a random effect Tobit model as implemented in Thiébaut and Jacqmin-Gaddausing SAS Proc NLMIXED[26,27] to impute missing AMH

values and those below the limit of detection. Because the automated assay was implemented in 2017, the new calibrated values were used to impute AMH values.

Based on the mean age of 55 years in our study and the variable timeframe of early perimenopause, women with detectable AMH were classified as pre-menopausal/early perimenopausal. Women who were 3 to 10 years from their first undetectable AMH level were classified as early menopausal per the STRAW+10 criteria, and those who were >10 years from their first undetectable AMH were classified as menopausal.

Inflammatory and immune activation markers

We focused on inflammatory and immune activation markers that have been associated with stroke and cardiovascular disease in HIV and non-HIV populations[28–37]. We tested inflammatory and immune activation markers in cryopreserved biospecimens from the most recent WIHS visit preceding the TCD study. IL-6 and CRP were measured in plasma samples using a multiplex electrochemiluminescence assay (Meso Scale Discovery, MD, USA). Soluble CD14 (R&D Systems, MN, USA) and CD163 (Aviscera Bioscience, CA, USA) were measured by ELISA. Details of peripheral blood mononuclear cell (PBMC) laboratory testing have been described previously[38]. Cryopreserved PBMCs were thawed in batches and stained with viability dye LIVE/DEAD® Fixable Blue Dead Cell Stain Kit (Life Technologies, NY, USA). Cells were washed and stained with fluorescent conjugated antibodies for cell surface markers. To measure CD4+ and CD8+ T cell activation and identify monocytes, PBMCs were stained as described previously[38]. Subpopulations of monocytes were evaluated with stains for anti-CD14 FITC (eBioscience, CA, USA), anti-CD16 PE-Cy7 (Biolegend, CA, USA), anti-CCR2 PerCPCy5.5 (Biolegend), anti-CX3CR1 APC (Biolegend), anti-CD163 PE (R&D systems) and anti-CCR5 APC-Cy7 (BD, NJ, USA). Cellular markers were detected by flow cytometry using LSRII flow cytometer (BD).

Statistical analyses

We compared demographic and clinical characteristics between WWH and women at risk for HIV and WWH and MWH using Student’s t, Wilcoxon rank-sum, Chi-square or Fisher’s exact test, as appropriate. We used mixed effects linear regression models, which included a random subject effect to account for within-person correlation. This was necessary because cerebral vasoreactivity was measured for the left and right middle cerebral artery for each participant. Models were first unadjusted and then adjusted for age and race/ethnicity to determine the association of HIV and other factors with cerebral vasoreactivity. All models were adjusted for change in mean arterial pressure with breath-holding, which can affect change in flow velocities. We constructed a separate model to identify factors associated with cerebral vasoreactivity in WWH. After combining data from WWH and MWH, we evaluated the effect of sex and other risk factors on cerebral vasoreactivity. In sensitivity analyses, we adjusted for estrogen use to account for the potential impact of estrogen on the observed association between sex, menopause and cerebral vasoreactivity. P values were two-sided with 0.05 considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, NC, USA).

Results

Demographic and clinical characteristics of 33 WWH, 16 women at risk for HIV, and 37 MWH are shown in Table 1. The mean age of WWH and women at risk for HIV was similar (55 versus 53 years, p=0.34). There was no statistically significant difference in the distribution of race/ethnicity by HIV status among women. The median cardiovascular risk score was comparable between WWH and women at risk for HIV, although women at risk for HIV had higher indices of obesity. Mean cerebral vasoreactivity was similar in WWH and women at risk for HIV but lower than published reference norms for this age range[21].

On average, WWH were younger than men (55 versus 61 years, p=0.002). In addition, nearly three quarters of WWH were non-white, whereas 84% of men were white. WWH were less likely to be on a statin, more likely to be current smokers, and had higher total, LDL, and HDL cholesterol compared with men (Table 1).

In demographics-adjusted models in women (Table 2), a statistically significant association was not observed between HIV and cerebral vasoreactivity. A history of CHD was significantly associated with lower cerebral vasoreactivity, as was HCV. Menopausal status appeared to have little association with cerebral vasoreactivity (Table 2), even after accounting for estrogen use (−0.07 for late peri/post-menopause versus pre-/early perimenopause, 95% CI −0.47 to +0.33, p=0.73). Of the inflammatory and immune activation markers (Figure 1), higher sCD163 was associated with a trend toward lower cerebral vasoreactivity (−0.19 per doubling, 95% CI −0.40 to +0.02, p=0.075). A higher proportion of CX3CR1+ CD4+ T cells was significantly associated with lower cerebral vasoreactivity (−0.16 per doubling, 95% CI −0.29 to −0.02, p=0.023).

When the analysis was restricted to WWH, women with a higher cardiovascular risk score had significantly lower cerebral vasoreactivity (Figure 2), even after adjusting for age and race/ethnicity (Table 2). Among individual risk factors, a history of CHD was significantly associated with cerebral vasoreactivity, as were HCV and estrogen use. Again, menopausal status appeared to have little association with cerebral vasoreactivity (Table 2), even after adjusting for estrogen use (+0.22 for late peri/post-menopausal versus pre-/early perimenopausal, 95% CI −0.12 to +0.56, p=0.20). Higher sCD163 was associated with lower cerebral vasoreactivity (−0.20 per doubling of sCD163, 95% CI −0.39 to −0.02, p=0.033). Doubling of the percentage of CD4+ T cells expressing CX3CR1 was associated with −0.14 lower cerebral vasoreactivity (95% CI −0.25 to −0.02, p=0.028). No other statistically significant associations were observed between inflammatory and immune activation markers and cerebral vasoreactivity (Figure 1).

In an unadjusted model that included WWH and MWH (Table 3), there was no statistically significant difference in cerebral vasoreactivity between women and men. After adjusting for age and race/ethnicity, female sex was associated with a trend toward higher cerebral vasoreactivity, indicating better cerebrovascular function than men, although the trend was no longer present after excluding the 3 WWH on estrogen (+0.13, 95% CI −0.10 to +0.36, p=0.26). Black and other race/ethnicity were associated with lower cerebral vasoreactivity compared with white race, as was HCV (Table 3). CHD appeared to be only weakly

associated with lower cerebral vasoreactivity in the pooled model of WWH and men (Table 3), unlike in the women-only model in which CHD had a strong negative association (Table 2).

Discussion

We did not find a statistically or clinically significant difference in cerebral vasoreactivity between virologically suppressed WWH and women at risk for HIV. Women in the cohort, whose mean age was 54 years, had cerebral vasoreactivity values comparable to previously published norms for women 70 years of age and older[21], which may reflect the fact that we selected for participants at higher cardiovascular risk. Unlike our prior findings from a men-only cohort, virologically suppressed HIV may not be associated with lower cerebral vasoreactivity in women. Alternatively, the effect of HIV on cerebral vasoreactivity may have been overshadowed by the impact of cardiovascular risk, particularly given the higher prevalence of several cardiometabolic risk factors (e.g., current smoking, hypertension, obesity) among women at risk for HIV compared with WWH. In a comparable study of cerebral vasoreactivity in PWH in China, we found that the contribution of HIV to cerebrovascular dysfunction was most pronounced in individuals at lower traditional cardiovascular risk[14]. As PWH age, the negative consequences of HIV on cerebrovascular risk may be eclipsed by the effect of cardiovascular comorbidities[2,39], underscoring the importance of aggressive cardiovascular risk factor modification in this patient population. This may be especially critical for women given evidence supporting a greater increase in stroke risk conferred by HIV in women compared with men[1]. Similar to findings from other cohorts[40], however, although WWH in the study had higher total and LDL cholesterol and were more likely to smoke compared with men, fewer were on a statin.

Menopausal status was not significantly associated with cerebral vasoreactivity in our study, even after accounting for estrogen use among menopausal women in the cohort. In general, estrogen depletion occurs when AMH, a marker of ovarian reserve independent of menstrual cycle phase, becomes undetectable. Based on prior studies in the general population that have found postmenopausal women to have lower cerebral vasoreactivity compared with premenopausal women independent of age[16], we hypothesized that women with undetectable AMH would have lower cerebral vasoreactivity and that HIV could modify the effect of estrogen depletion on cerebrovascular function, resulting in a greater decline in vasoreactivity. The small number of women with detectable AMH may have limited our ability to adequately investigate the relationship between menopause and cerebrovascular dysfunction. Contrary to our hypothesis, WWH had a trend toward higher cerebral vasoreactivity compared with MWH, suggesting that WWH had better cerebrovascular function than men despite an overall worse cardiovascular risk profile. The trend toward better cerebrovascular function in women, who were younger than men, persisted after adjusting for age but not after excluding the 3 WWH on estrogen.

By design, all participants in the study were at higher cardiovascular risk. When individual cardiometabolic risk factors were examined, only a history of CHD was associated with lower cerebral vasoreactivity among women. Although this finding remained significant when we restricted the analysis to WWH, the modest number of women with a history of

CHD precluded our ability to draw definitive conclusions. When cardiovascular risk was examined collectively using a cardiovascular risk score, the more cardiometabolic risk factors WWH had, the lower their cerebral vasoreactivity. This suggests that, while individual risk factors may not reach a threshold associated with worse cerebrovascular function, their joint effect may be sufficient to negatively impact cerebral vasoreactivity.

HCV infection was consistently associated with lower cerebral vasoreactivity, independent of age or race/ethnicity. The contribution of HCV to stroke risk in HIV has been examined in several cohort studies, with conflicting results[5,6,41,42]. We previously observed a trend toward lower cerebral vasoreactivity associated with HCV in MWH and men without HIV[13]. Because of the study's modest sample size, we were unable to adjust for potential confounders of the association between HCV and cerebrovascular function, including smoking and alcohol use, although neither of these factors was significantly associated with cerebral vasoreactivity.

Women with greater monocyte activation, as measured by sCD163, trended toward lower cerebral vasoreactivity. When the analysis was restricted to WWH, which resulted in a reduced sample size, the association between higher sCD163 and lower cerebral vasoreactivity was statistically significant. One possible explanation for the significant association among WWH is that HIV may accentuate the effect of monocyte activation on subclinical atherosclerosis and cerebrovascular risk. sCD163 has been linked to cardiovascular risk and mortality in PWH[30,32,33,43]. We also observed a significant association between the proportion of CD4+ T cells expressing the chemokine receptor, CX3CR1, and lower cerebral vasoreactivity. CX3CR1 has been implicated in the pathogenesis of atherosclerosis related to monocyte-macrophage trafficking in activated endothelium[44]. In addition, progression of carotid atherosclerosis in PWH has been associated with a high frequency of CX3CR1-expressing CD4+ T cells, many of which are cytomegalovirus (CMV)-specific[45]. CMV can stimulate transendothelial migration of pro-inflammatory CD4+ T cells by enhancing production of its ligand, CX3CL1, leading to accelerated atherosclerosis. Due to limited data on CMV serostatus in the cohort, we were unable to explore the hypothesis that CMV co-infection might be driving worse cerebrovascular function by enhancing the expansion of CD4+ T cells expressing CX3CR1.

A major limitation of the study was the modest sample size, which may impact the reliability of our findings. Additionally, because of the sample size, we were unable to use multivariable modeling to understand the independent effect of covariates on cerebral vasoreactivity. By selecting for older women at least 40 years of age, we had few participants who were pre-menopausal, which constrained our investigation of differences in cerebral vasoreactivity by menopausal status. Furthermore, combining data from WWH and MWH to examine the effect of sex on cerebral vasoreactivity proved challenging. Despite attempting to frequency match recruited WWH to men who had already undergone TCD as part of an unrelated clinical trial, the characteristics of our study population differed significantly by sex. Women were younger than men and more likely to be black, reflecting the epidemiology of HIV in the US. Although we accounted for these differences in demographics-adjusted models, residual confounding may have been present. Moreover, the overall cardiovascular risk profile was worse in WWH compared with men, although we

would have expected this to bias toward women having worse cerebral vasoreactivity. Finally, by limiting cerebral vasoreactivity testing to the middle cerebral arteries, we may have missed regional differences in cerebrovascular function by HIV status[46].

Conclusion

In this study of older WWH, women at risk for HIV, and MWH, all at higher cardiovascular risk, WWH did not have significantly different cerebrovascular function compared with women without HIV. In this small sample, we believe that cardiovascular risk, which was elevated for all participants by virtue of the study design, may have overshadowed the potential negative effect of HIV on cerebrovascular function. This underscores the strong contribution of traditional cardiometabolic risk factors to cerebrovascular risk in women, including in WWH. We also did not find that WWH had lower cerebrovascular function than MWH. In fact, WWH had a trend toward higher cerebrovascular function, although the trend was no longer present after excluding women on estrogen replacement therapy. Comparisons between WWH and MWH were also limited by sex differences in age and other clinical characteristics. Large collaborative studies like the newly funded Multicenter AIDS Cohort Study/WIHS Combined Cohort Study will allow for robust research to investigate the mechanisms underlying observed sex differences in cerebrovascular risk in HIV. Strategies to adequately account for demographic and clinical dissimilarities present between WWH and MWH that may affect observed sex differences will be essential.

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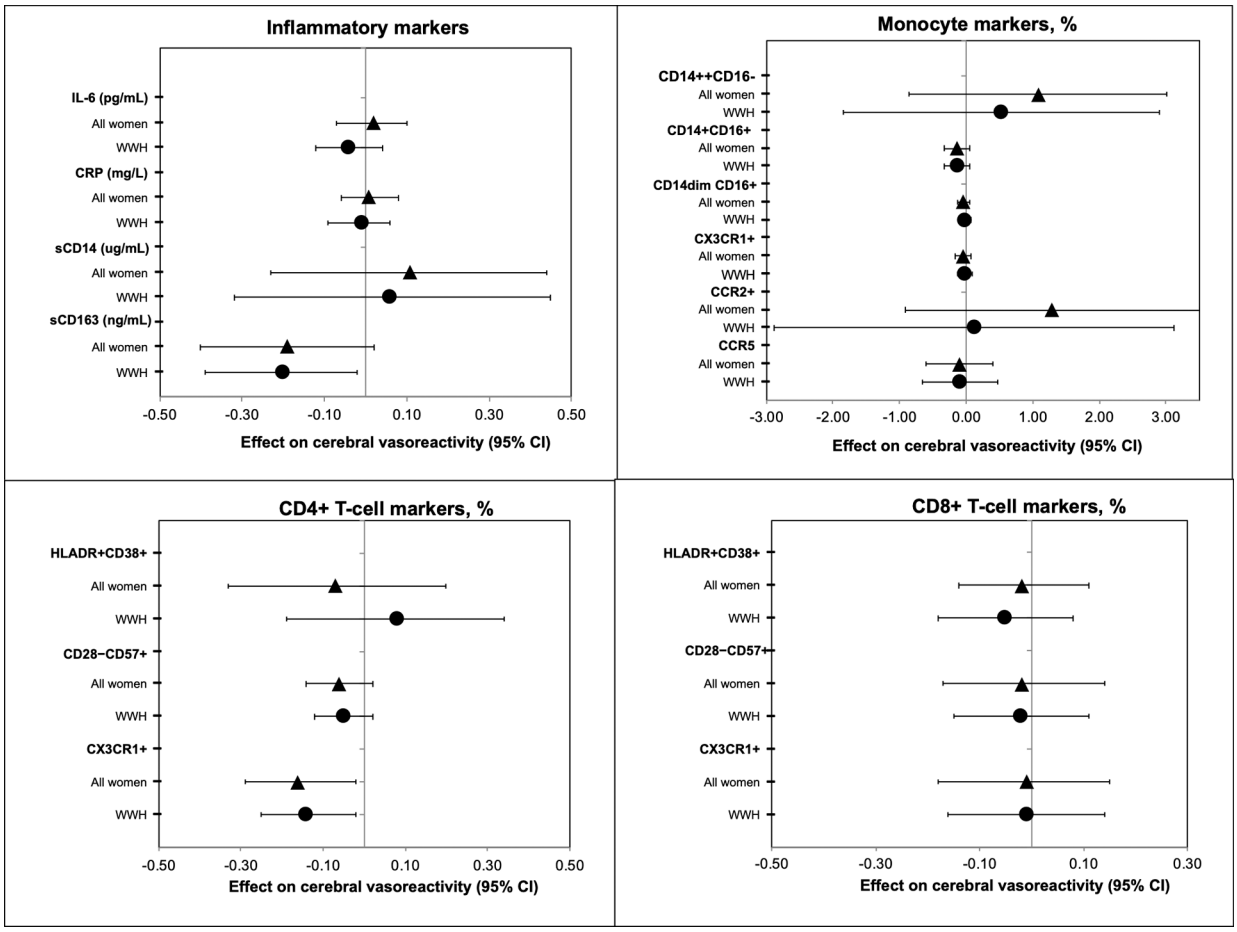

Figure 1.

Effect of inflammation and immune activation markers on cerebral vasoreactivity (measured by breath-holding index) among women with and without HIV (“All women”) and women with HIV (“WWH”). Estimates shown represent the effect on cerebral vasoreactivity per doubling of each inflammatory marker or per doubling of the percentage of cells expressing each immune activation marker.

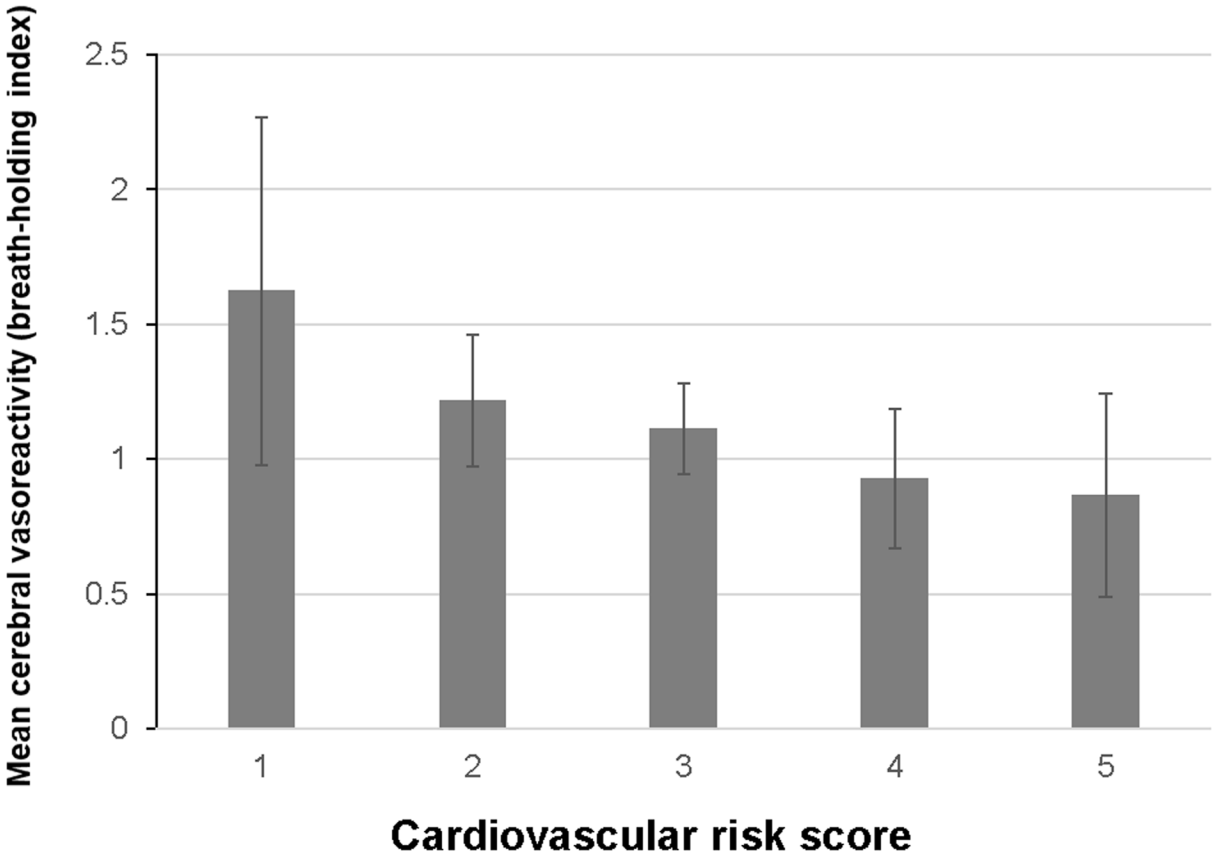

Figure 2.
Mean cerebral vasoreactivity (measured by breath-holding index) and standard deviation for women with HIV by cardiovascular risk score.

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Table 1:

Demographic and clinical characteristics

No. (%) unless otherwise noted	Women			Men	
	HIV (n=33)	HIV-seronegative (n=16)	P value*	HIV (n=37)	P value**
Sociodemographics					
Age (years), mean (SD)	55 (8)	53 (9)	0.34	61 (8)	0.002
Race/ethnicity					
White	9 (27)	2 (13)	0.24	31 (84)	<0.001
Black	13 (39)	11 (69)		3 (8)	
Hispanic/Other	11 (33)	3 (19)		3 (8)	
Cardiometabolic and other risk factors					
Hypertension	23 (70)	14 (88)	0.29	23 (62)	0.63
Diabetes mellitus	5 (15)	2 (13)	1.00	5 (14)	0.89
Coronary heart disease	2 (6)	2 (13)	0.59	5 (14)	0.43
Prior stroke	0 (0)	1 (6)	0.33	0 (0)	1.00
Statin use	5 (15)	2 (13)	1.00	18 (49)	0.006
Total cholesterol (mg/dL), mean (SD)	201 (50)	188 (41)	0.38	166 (31)	0.001
HDL cholesterol (mg/dL), mean (SD)	52 (17)	56 (18)	0.52	44 (12)	0.022
LDL cholesterol, (mg/dL), mean (SD)	116 (40)	106 (36)	0.36	92 (22)	0.003
Body mass index (kg/m^2) mean (SD)	30 (7)	34 (7)	0.040	---	---
Waist circumference (cm), mean (SD)	101 (12)	113 (16)	0.005	---	---
Hepatitis C infection	5 (15)	0 (0)	0.16	5 (14)	0.99
Current smoker	9 (27)	7 (44)	0.25	3 (8)	0.039
Number of pack years, median (IQR)	1 (0, 9)	5 (0, 9)	0.50	---	---
Current alcohol use	13 (39)	9 (56)	0.27	14 (38)	0.77
Cardiovascular risk score***, median (IQR)	2 (2, 3)	2 (2, 3)	0.32	2 (1, 2)	0.030
Menopausal status and estrogen replacement					
Estimated AMH level at TCD study visit (ng/mL), mean (SD)	0.04 (0.07)	0.10 (0.12)	0.030	---	---
Menopausal status based on AMH level at TCD study visit****			0.090	---	---
Pre-menopausal + early perimenopausal	6 (19)	6 (38)			

No. (%) unless otherwise noted	Women			Men	
	HIV (n=33)	HIV-seronegative (n=16)	P value*	HIV (n=37)	P value**
Late perimenopausal	3 (10)	1 (6)			
Early menopausal	8 (26)	7 (44)			
Menopausal	14 (45)	2 (13)			
Estrogen replacement therapy	3 (9)	0 (0)	0.54		
HIV-related risk factors					
CD4 count (cells/mm^3), mean (SD)	811 (262)	---	---	709 (240)	0.092
Nadir CD4 count (cells/mm^3), mean (SD)	218 (134)	---	---	212 (132)	0.85
HIV RNA ≤40 copies/ml	33 (100)	---	---	37 (100)	1.00
HIV duration (years), median (IQR)	21 (14, 22)	---	---	26 (23, 31)	<0.001
Cerebral vasoreactivity, mean (SD)	1.13 (0.40)	1.13 (0.70)	1.00	1.05 (0.35)	0.25

Abbreviations: AMH, anti-Mullerian hormone

*Comparing women with and without HIV

**Comparing women and men with HIV

***Cardiovascular risk score = number of cardiometabolic risk factors per participant

****Data were not available for 2 of the 33 women with HIV

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Table 2:

Effect of cardiometabolic and other risk factors on cerebral vasoreactivity (measured by breath-holding index) in women

	Women with and without HIV (n=49)				Women with HIV only (n=33)			
Effect on cerebral vasoreactivity (95% CI)	**Unadjusted**	**P value**	**Demographics-adjusted**	**P value**	**Unadjusted**	**P value**	**Demographics-adjusted**	**P value**
HIV infection	−0.10 (−0.39, +0.18)	0.47	−0.11 (−0.40, +0.18)	0.44	---	---	---	---
Age (*per 10 years*)	+0.10 (−0.10, +0.26)	0.20	+0.10 (−0.04, +0.30)	0.12	+0.03 (−0.12, +0.19)	0.65	+0.01 (−0.20, +0.20)	0.86
Race/ethnicity								
Black	+0.003 (−0.33, +0.34)	0.99	+0.07 (−0.27, +0.41)	0.69	−0.16 (−0.48, +0.16)	0.32	−0.15 (−0.50, +0.20)	0.38
Hispanic	−0.15 (−0.57, +0.27)	0.47	−0.16 (−0.57, +0.25)	0.44	−0.09 (−0.44, +0.26)	0.61	−0.09 (−0.45, +0.27)	0.61
Other	−0.33 (−0.78, +0.13)	0.15	−0.30 (−0.75, +0.15)	0.18	−0.37 (−0.81, +0.06)	0.089	−0.37 (−0.81, +0.08)	0.10
Hypertension	−0.08 (−0.38, +0.22)	0.59	−0.09 (−0.40, +0.22)	0.57	−0.17 (−0.44, +0.09)	0.19	−0.17 (−0.45, +0.11)	0.23
Diabetes	−0.05 (−0.42, +0.32)	0.80	+0.01 (−0.40, +0.42)	0.96	−0.19 (−0.53, +0.16)	0.28	−0.21 (−0.61, +0.19)	0.28
Coronary heart disease	−0.51 (−0.96, −0.06)	0.027	−0.55 (−1.01, −0.09)	0.020	−0.43 (−0.93, +0.06)	0.085	−0.63 (−1.18, −0.07)	0.030
Statin use	−0.01 (−0.40, +0.39)	0.98	+0.02 (−0.39, +0.43)	0.93	+0.08 (−0.27, +0.42)	0.64	+0.10 (−0.27, +0.46)	0.59
Cardiovascular risk score (*per 1 additional cardiometabolic risk factor*)	−0.11 (−0.26, +0.03)	0.13	−0.12 (−0.27, +0.04)	0.13	−0.15 (−0.27, −0.02)	0.020	−0.14 (−0.28, −0.01)	0.038
Body mass index (*per 5 kg/m*^{2})	+0.02 (−0.07, +0.12)	0.60	+0.01 (−0.01, +0.03)	0.33	−0.002 (−0.09, +0.09)	0.96	+0.003 (−0.10, +0.10)	0.96
Waist circumference (*per 5* cm)	+0.02 (−0.02, +0.07)	0.27	−0.04 (−0.01, +0.08)	0.11	+0.01 (−0.04, +0.07)	0.57	+0.02 (−0.04, +0.07)	0.54
Current smoker	−0.17 (−0.47, +0.13)	0.25	−0.24 (−0.56, +0.08)	0.14	−0.20 (−0.49, +0.09)	0.17	−0.19 (−0.52, +0.14)	0.25
Smoking (*per pack-year*)	−0.02 (−0.04, +0.001)	0.057	−0.02 (−0.04, +0.01)	0.12	+0.002 (−0.03, +0.03)	0.30	−0.01 (−0.03, +0.02)	0.57
Current alcohol use	+0.01 (−0.25, +0.27)	0.94	−0.01 (−0.27, +0.25)	0.93	+0.03 (−0.22, +0.29)	0.79	+0.03 (−0.24, +0.29)	0.85
Hepatitis C infection	−0.29 (−0.71, +0.13)	0.17	−0.42 (−0.84, −0.003)	0.049	−0.28 (−0.61, +0.05)	0.092	−0.40 (−0.73, −0.06)	0.024
Estimated AMH level at TCD study visit (*per doubling*)	−0.01 (−0.05, +0.03)	0.49	+0.04 (−0.05, +0.12)	0.38	−0.02 (−0.06, +0.02)	0.23	−0.08 (−0.18, +0.01)	0.07
Late perimenopausal + menopausal vs. pre-menopausal + early perimenopausal	+0.11 (−0.18, +0.39)	0.46	−0.05 (−0.46, +0.36)	0.79	+0.16 (−0.12, +0.44)	0.24	+0.24 (−0.15, +0.62)	0.22
Estrogen replacement therapy	+0.54 (+0.03, +1.06)	0.039	+0.44 (−0.09, +0.97)	0.10	+0.59 (+0.21, +0.96)	0.003	+0.58 (+0.17, +0.99)	0.007
CD4 count (*per 100 cell/mm*^{3})	---	---	---	---	+0.001 (−0.06, +0.04)	0.58	0 (−0.06, +0.06)	1.00
Nadir CD4 (*per 100 cell/mm*^{3})	---	---	---	---	+0.001 (−0.09, +0.10)	0.99	+0.004 (−0.10, +0.11)	0.93
HIV duration (*per 10 years*)	---	---	---	---	+0.13 (−0.06, +0.32)	0.17	+0.14 (−0.08, +0.36)	0.19

Table 3:

Effect of sex, cardiometabolic, HIV-related and other risk factors on cerebral vasoreactivity (measured by breath-holding index) in women and men with HIV

Effect on cerebral vasoreactivity (95% CI)	Combined Women and Men with HIV (n=70)			
	Unadjusted	P value	Demographics-adjusted	P value
Female sex	+0.06 (−0.13, +0.24)	0.54	+0.20 (−0.02, +0.42)	0.078
Age (*per 10 years*)	+0.01 (−0.10, +0.12)	0.80	−0.02 (−0.10, +0.10)	0.73
Race/ethnicity (*vs. White*)				
Black	−0.22 (−0.43, −0.004)	0.046	−0.37 (−0.61, −0.12)	0.004
Hispanic/Latino	+0.06 (−0.22, +0.34)	0.65	−0.07 (−0.37, +0.24)	0.66
Other	−0.31 (−0.65, +0.04)	0.081	−0.42 (−0.78, −0.06)	0.022
Hypertension	−0.05 (−0.24, +0.14)	0.62	+0.01 (−0.18, +0.20)	0.93
Diabetes	−0.10 (−0.36, +0.15)	0.42	−0.13 (−0.39, +0.14)	0.35
Coronary heart disease	−0.07 (−0.37, +0.23)	0.64	−0.17 (−0.47, +0.13)	0.26
Statin use	+0.04 (−0.15, +0.23)	0.71	+0.02 (−0.18, +0.23)	0.84
Current smoker	−0.19 (−0.43, +0.05)	0.12	−0.08 (−0.37, +0.22)	0.61
Current alcohol use	−0.06 (−0.25, +0.12)	0.50	−0.04 (−0.22, +0.15)	0.68
Cardiovascular risk index (*per 1 additional cardiometabolic risk factor*)	−0.05 (−0.15, +0.04)	0.25	−0.03 (−0.12, +0.07)	0.56
Hepatitis C infection	−0.23 (−0.48, +0.02)	0.073	−0.28 (−0.52, −0.03)	0.028
CD4 count (*per 100 cell/mm^3*)	+0.01 (−0.03, +0.04)	0.73	+0.02 (−0.02, +0.06)	0.30
Nadir CD4 (*per 100 cell/mm^3*)	−0.01 (−0.07, +0.05)	0.85	−0.01 (−0.07, +0.05)	0.71
HIV duration (*per 10 years*)	+0.03 (−0.08, +0.15)	0.56	+0.01 (−0.12, +0.15)	0.84