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Cerebral vasoreactivity is impaired in treated, virally suppressed HIV-infected individuals

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Abstract

Objective—To compare cerebral vasoreactivity, a measure of cerebrovascular endothelial function, between treated, virally suppressed HIV-infected individuals and HIV-uninfected controls and to evaluate the effect of HIV-specific factors on cerebral vasoreactivity.

Methods—Cross-sectional study of 65 antiretroviral therapy (ART)-treated, virally suppressed HIV-infected individuals and 28 HIV-uninfected controls. Participants underwent noninvasive assessment of cerebral vasoreactivity using transcranial Doppler ultrasound and inhaled carbon

Author contributions

F.C.C. participated in the study concept and design, performed the data analysis and interpretation and drafted and revised the manuscript. W.J.B. performed the data analysis and interpretation and preparation and revision of the manuscript. C.M. and C.C. participated in data collection and preparation and revision of the manuscript. N.K., R.W.P. and S.D. contributed to data interpretation and preparation and revision of the manuscript. F.A.S. contributed to study design, data interpretation and preparation and revision of the manuscript. P.Y.H. supervised study design, data analysis and interpretation, and preparation and revision of the manuscript.

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dioxide (CO_2). We used mixed effects multivariable linear regression to determine the association of HIV infection and HIV-specific factors with cerebral vasoreactivity.

Results—Mean age was 57.2 years for HIV-infected participants and 53.5 years for HIV-uninfected controls. Most participants (95%) were men. 26% of HIV-infected participants were non-white compared with 32% of controls. Among HIV-infected participants, mean CD4 count was 596 cells/mm^3, and mean duration of viral suppression was 7.8 years. Cerebral vasoreactivity in response to hypercapnia (cerebral VR_{hyper}) was lower in HIV-infected individuals compared with uninfected controls (3.23% versus 3.81%, p=0.010). After adjusting for demographic and vascular risk factors, HIV infection was independently associated with lower cerebral vasoreactivity (−0.86%, 95% CI −1.30% to −0.42%, p<0.001). We did not find a statistically significant effect of recent or nadir CD4 count on cerebral vasoreactivity. There was a trend toward higher cerebral vasoreactivity for each additional year of viral suppression.

Conclusions—Treated, virally suppressed HIV infection negatively impacted cerebral vasoreactivity even after adjustment for traditional vascular risk factors. These data highlight the potential contribution of cerebrovascular endothelial dysfunction to the elevated risk of stroke observed in HIV-infected individuals.

Keywords

HIV; treatment; cerebrovascular disease; stroke; cerebral vasoreactivity; endothelial function; transcranial Doppler

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With the transformation of HIV into a chronic, treatable disease, HIV-infected individuals face excess risk of a growing number of non-AIDS-related comorbidities more typical of an aging population.[1,2] Rates of several vascular outcomes, including stroke, are higher in HIV-infected individuals than in age-matched uninfected controls.[3–7] Endothelial dysfunction and accelerated atherosclerosis related to HIV-associated chronic inflammation and immune activation may contribute to increased cardiovascular risk in this unique patient population.[8] The mechanisms underlying increased cerebrovascular risk in HIV infection, however, have not been investigated. Cerebrovascular function in individuals with treated, virally suppressed chronic HIV infection is unknown, including whether it is impaired compared with HIV-uninfected individuals.

Cerebral vasoreactivity (VR) is a measure of cerebrovascular endothelial function associated with both small vessel and severe large artery cerebrovascular injury.[9–14] Measurement of cerebral VR with transcranial Doppler (TCD) ultrasound is non-invasive, cost-effective and has excellent temporal resolution. A vasodilatory response to inhaled carbon dioxide (CO_2) and vasoconstriction to hyperventilation, denoted by an increase and decrease in mean blood flow velocity of the cerebral arteries, respectively, is one method of assessing cerebral VR. Changes in cerebral VR over time and in response to interventions aimed at improving cerebrovascular function can be readily monitored. For example, cerebral VR has been shown to improve with interventions that reduce cerebrovascular risk, including statin use and exercise.[15–17]

The primary goal of the UNderstanding Cerebral VasoReactivity in HIV infection (UNCoVeR) study was to compare cerebral VR between treated, virally suppressed HIV-

infected individuals and uninfected controls and to evaluate the effect of HIV-specific factors on cerebral VR.

Methods

Study population

We performed a cross-sectional study of a convenience sample of participants from SCOPE[18] (the Study of the Consequences of the Protease Inhibitor Era), a contemporary cohort of over 2000 HIV-infected individuals and uninfected controls followed prospectively at San Francisco General Hospital. Participants involved in a parent study evaluating cardiovascular health in HIV infection in SCOPE were contacted to gauge interest in participation in a sub-study focused on cerebrovascular risk. Original recruitment for the parent study occurred at routine SCOPE visits, where participants received information regarding the cardiovascular study and, if interested, contacted the study for additional details. Demographically-matched uninfected controls were recruited for the parent study through referrals of friends and acquaintances of HIV-infected participants and were tested for HIV prior to entry. Flyers were also posted around the hospital and outpatient clinics advertising the parent study. All participants were at least 18 years of age and willing to abstain from caffeine, tobacco, alcohol or other substance use for 12 hours prior to the study. The study was approved by the University of California, San Francisco Committee on Human Research.

All HIV-infected participants were on a stable antiretroviral therapy (ART) regimen with undetectable plasma HIV RNA (<40 copies/mL) for a minimum of 24 weeks prior to the study. Exclusion criteria included: 1) a history of stroke or transient ischemic attack, central nervous system infection or traumatic brain injury in the 3 months before the study; 2) a history of intracranial vasculitis or arteriopathy due to causes other than HIV or traditional vascular disease (e.g., primary CNS vasculitis); 3) use of immune modulatory agents in the 3 months before the study; 4) absent temporal acoustic windows; 5) a history of an untreated cerebral aneurysm or other vascular malformation, severe chronic obstructive pulmonary disease, unstable angina, recent myocardial infarction or other conditions that precluded cerebral VR testing.

Cerebral vasoreactivity

We assessed cerebral VR with the CO_2 challenge test.[19] TCD was used to measure alterations in middle cerebral artery (MCA) mean blood flow velocity in response to changes in end-tidal CO_2 ($ETCO_2$). A single vascular technologist trained in the TCD CO_2 challenge test and blinded to HIV status performed all studies to minimize interrater variability. A Sonara Digital TCD machine (Natus Medical, San Carlos, CA) was used for all studies. The MCA signal was identified through a transtemporal approach using standard methodology[20,21]. We recorded mean blood flow velocities at rest, during inhalation of a 6% CO_2 gas mixture and during mild hyperventilation.

The primary cerebral VR outcome was cerebral VR in response to hypercapnia (cerebral VR_{hyper}), defined as the percentage change in mean flow velocity from baseline to induced

hypercapnia per unit change in $ETCO_2$. As a secondary outcome, we also evaluated cerebral VR in response to the full range of hyper- and hypocapnia (cerebral $VR_{hyper + hypo}$), calculated as the percentage change in mean flow velocity from hypercapnia to hypocapnia per unit change in $ETCO_2$.

We performed repeat cerebral VR testing within one month of the first procedure to assess reproducibility in 5 participants. For the repeat study, participants were scheduled at approximately the same time of day as the first procedure to minimize diurnal variability. Because cerebral VR for the left and right sides were highly correlated, we compared a single value representing the mean cerebral VR from the left and right sides between the first and second visits. We calculated the intraclass correlation coefficient (ICC) after adjusting for the change in mean arterial pressure with induced hypercapnia. We found a strong correlation between cerebral VR from the first and second visits, although the large confidence intervals reflect the small number of repeated studies performed (ICC for cerebral VR_{hyper} of 0.80, 95% CI 0.30 to 0.97; ICC for cerebral $VR_{hyper + hypo}$ of 0.93, 95% CI 0.65 to 0.99).

Vascular risk factors, substance use and other covariates

Prior to the TCD study, we collected data on comorbidities and other covariates that could potentially confound or mediate the association between HIV infection and cerebral VR, including traditional vascular risk factors (defined by self-report of prior diagnosis by a medical provider with or without current use of anti-hypertensive, anti-diabetic or lipid-lowering therapy); anti-platelet and statin use; current smoking, alcohol and substance use; and a history of migraines and sleep apnea. HIV-specific characteristics, including duration of HIV infection and viral suppresion, ART use by class, most recent and nadir CD4 count, were also obtained. These data were supplemented and/or confirmed by available information through the parent cardiovascular study and review of electronic medical records.

Statistical analysis

We compared demographic and clinical characteristics between HIV-infected and uninfected participants using t-test, Chi-square test or Fisher's exact test. We used mixed effects linear regression models to determine the association between HIV and cerebral VR and between HIV-specific factors and cerebral VR. Because cerebral VR is measured on the left and right sides, we included a random person effect to account for within-person correlation. All multivariable models were adjusted for age and race. In the models of HIV-infected individuals and uninfected controls, we included clinically relevant covariates of *a priori* interest (e.g., hypertension, diabetes mellitus, statin use) and other covariates chosen by forward stepwise selection. To maximize parsimony in the HIV-only analyses (given fewer observations), only covariates identified through forward stepwise selection were included. *P* values were 2-sided with ≤ 0.05 considered statistically significant. Statistical analyses were performed using Stata (StataCorp 2012. Stata Statistical Software: Release 12; Stata Corporation, College Station, TX).

Results

Study enrollment

We enrolled 100 individuals between January and June 2014 who underwent the TCD CO_2 challenge. Of these 100 individuals, one participant terminated the study early due to discomfort from breathing into the mouthpiece. In one HIV-infected participant, an acoustic temporal window on neither the left nor right sides could be located. In one control participant, we did not observe an adequate rise in $ETCO_2$ following inhalation of the CO_2 gas mixture, which was hypothesized to be from a poor seal around the mouthpiece due to a preexisting neurological illness. In 4 participants (3 HIV-infected and 1 control), cerebral VR results were excluded because the expected rise or fall in mean blood flow velocities during inhalation of CO_2 or mild hyperventilation was not observed. In sum, the results from 93 participants were included in the study (65 HIV-infected and 28 uninfected control participants), on whom 175 total (87 left-sided 88 right-sided) measurements were obtained.

Baseline demographic and clinical characteristics

Demographic and clinical characteristics of the 93 participants are included in Table 1. HIV-infected participants were older than uninfected controls, although this did not reach statistical significance. Most participants were men, while 26% of HIV-infected participants were non-white compared with 32% of controls. Several vascular risk factors were more common in HIV-infected participants, including hypertension (49 versus 29%, p=0.065), dyslipidemia (57 versus 21%, p-0.002) and diabetes mellitus (12 versus 0%, p-0.10). Statin and aspirin use were also more common among HIV-infected participants. More uninfected controls were current alcohol users, while marijuana use was more common among HIV-infected participants. Among the HIV-infected cohort, the mean CD4 count was 596 cells/mm^3, while the mean nadir CD4 count was 242 cells/mm^3. The mean duration of known HIV seropositivity was 20.2 years, and mean duration of viral suppression was 7.8 years. Nearly all participants were on an ART regimen that contained at least one nucleoside reverse transcriptase inhibitor (NRTI) and 32% were on abacavir, while over half were on a non-nucleoside reverse transcriptase inhibitor (NNRTI) compared with 42% on a protease inhibitor and 34% on an integrase inhibitor.

Baseline mean blood flow velocities

Baseline mean blood flow velocity on the right and left sides for HIV-infected individuals were 52 cm/s and 53 cm/s, respectively, compared with 51 cm/s bilaterally for uninfected controls (p=0.65 for the right side, p=0.37 for the left side). As expected, intra-participant right and left-sided cerebral VR_{hyper} and cerebral $VR_{hyper + hypo}$ measurements were strongly correlated [Pearson correlation coefficients 0.85 (p<0.001) and 0.93 (p<0.001), respectively].

Difference in cerebral VR by HIV status

Cerebral VR_{hyper} was reduced in HIV-infected individuals compared with uninfected controls (cerebral VR_{hyper} 3.23%, 95% CI 2.98% to 3.47% compared with 3.81%, 95% CI 3.44% to 4.18%, p=0.010)(Table 2). After adjustment for age, race, diabetes mellitus,

hypertension, statin use, aspirin use, alcohol consumption and methamphetamine use, HIV infection was independently associated with lower cerebral VR (−0.86%, 95% CI −1.30% to −0.42%, p<0.001)(Figure 1, Table 2). Diabetes mellitus and non-white race were also independent predictors of lower cerebral VR_{hyper}, as was methamphetamine use (Table 2). Each additional drink per day was associated with an increase in cerebral VR_{hyper}. In the multivariate model of cerebral VR_{hyper}, we observed an interaction between statin use and HIV infection. Statin use among those with HIV infection was associated with an improvement in cerebral VR_{hyper}, while it had no statistically significant impact on cerebral VR_{hyper} among uninfected controls (Table 2). We observed a trend toward an association between hepatitis C infection and cerebral VR_{hyper} in a univariate model (Table 2) but not in the multivariate model. To check for stability of the final multivariate model, we performed adjusted models excluding several variables that affected a relatively small number of participants (e.g., diabetes mellitus, methamphetamine and statin use). In these simpler models, the main effect of HIV infection on cerebral VR was highly comparable to the full model.

In a secondary analysis, unadjusted cerebral $VR_{hyper + hypo}$ was lower in HIV-infected individuals compared with uninfected controls, although confidence intervals were too wide to rule out no difference in cerebral $VR_{hyper + hypo}$ by HIV status (2.23%, 95% CI 2.09% to 2.39% compared with 2.44%, 95% CI 2.21% to 2.67%, p=0.15)(Table 3). After adjusting for age, race, diabetes mellitus, hypertension, statin use, aspirin use, alcohol consumption, and methamphetamine use, HIV infection was independently associated with a reduction in cerebral $VR_{hyper + hypo}$ (−0.30%, 95% CI −0.56% to −0.03%, p=0.030)(Figure 1, Table 3). In the multivariate model, statin use was strongly associated with an increase in cerebral $VR_{hyper + hypo}$ (+0.42%, 95% CI +0.13% to +0.71%, p=0.004) as was alcohol use (+0.19% for each additional drink per day, 95% CI +0.04% to +0.33%, p=0.012), while diabetes mellitus was associated with a reduction in cerebral $VR_{hyper + hypo}$ (−0.46%, 95% CI −0.91% to −0.01%, p=0.047)(Table 3).

Risk factors for impaired cerebral VR among the HIV-infected cohort

In a multivariate model restricted to HIV-infected individuals, non-white race and diabetes mellitus were associated with lower cerebral VR_{hyper}, while statin use predicted higher cerebral VR_{hyper}. There was a trend toward an association between longer duration of viral suppression and higher cerebral VR_{hyper} (Table 4). We did not find a statistically significant effect of most recent or nadir CD4 count, duration of HIV infection or ART class on cerebral VR_{hyper}. In a multivariate model of the secondary outcome, cerebral $VR_{hyper + hypo}$, a CD4 count greater than 500 (+0.33%, 95% CI +0.03% to +0.62%, p=0.032) and longer mean duration of viral suppression (+0.04% for each additional year of suppression, 95% CI −0.001% to +0.08%, p=0.053) were associated with higher cerebral $VR_{hyper + hypo}$. In an exploratory analysis in which we stratified the HIV-only model by statin use to investigate the effect of HIV-related and other factors (adjusted for age and race) on participants not exposed to statins, longer mean duration of HIV infection was associated with worse cerebral VR_{hyper} (−0.05% for each additional year of infection, 95% CI −0.09% to −0.01%, p=0.026) among non-statin users. Current tobacco use also correlated with a reduction in cerebral VR_{hyper} (−0.67%, 95% CI −1.33% to −0.01%, p=0.045) among non-statin users.

Discussion

The primary goal of our study was to evaluate the association between well-controlled HIV infection and cerebral VR, a measure of cerebrovascular function. We found that cerebral VR was reduced in treated, virally suppressed HIV-infected individuals independent of traditional vascular risk factors that can impact cerebral VR, including hypertension and diabetes mellitus. These results suggest that treated HIV infection may confer additional cerebrovascular risk beyond that explained by comorbid traditional vascular risk factors.

Few studies have been performed investigating cerebral VR in HIV-infected individuals. One study from early in the treatment era evaluated cerebral VR using acetazolamide as the vasodilatory stimulus in 27 HIV-infected individuals and 10 uninfected controls.[22] The study participants were a heterogeneous group of HIV-infected individuals (6 met criteria for Centers for Disease Control and Prevention (CDC) clinical stage A, 16 clinical stage B and 7 clinical stage C) with a shorter duration of known HIV infection (mean duration 4.0 years) and worse immunodeficiency (mean CD4 count 217 cells/mm^3) compared with our cohort. Mean cerebral VR was statistically significantly lower in the HIV-infected group compared with uninfected controls. However, minimal clinical information, such as ART use or comorbid vascular risk factors, was available for comparison.

To our knowledge, this is the first study assessing cerebral VR in treated, virally suppressed HIV-infected individuals. Even among individuals with well-controlled HIV infection, which increasingly reflects the HIV population with access to ART, we observed reduced cerebral VR when compared to demographically-matched HIV-uninfected controls. Chronic HIV infection and its long-term inflammatory and immunologic effects may contribute to impaired cerebral vasodilatation at the arteriolar level in response to hypercapnia, which reflects intracranial endothelial dysfunction.[23–25] While few data are available regarding cerebrovascular endothelial function in HIV infection, findings from this study can be viewed in parallel with results from studies demonstrating systemic endothelial dysfunction, a marker of cardiovascular risk often evaluated with flow-mediated dilatation (FMD) of the brachial artery, in HIV-infected individuals. FMD is impaired in ART-naïve HIV-infected individuals, and rapidly improves after initiation of ART.[26] However, even among ART-treated individuals with well-controlled HIV infection, systemic endothelial function remains impaired. In participants from the parent study evaluating cardiovascular health in SCOPE from which our cohort was drawn, ART-treated HIV-infected individuals with undetectable HIV viral load had worse endothelial function compared with healthy controls.[27] Persistent systemic endothelial dysfunction in well-controlled HIV infection is hypothesized to be due to inflammatory and immune consequences of chronic HIV infection, which do not fully normalize despite virologic suppression and immune reconstitution on ART.[28–30] HIV “elite controllers,” a unique group of untreated HIV-infected individuals with undetectable viral load who lack the potential confounding effect of ART, also demonstrate increased inflammation, immune activation and atherosclerosis compared with HIV-uninfected controls, even after adjustment for traditional vascular risk factors.[31,32]

Hyperemic velocity, which reflects microvascular endothelial function, has been correlated with systemic markers of inflammation in HIV-infected individuals.[33] While we observed a trend toward an association between longer duration of viral suppression and higher cerebral VR, markers of immune activation and inflammation, which were not available for this study, would be more informative in future studies. In an exploratory analysis, we stratified the HIV-infected cohort by statin use to examine whether the effect of HIV-specific factors on cerebral VR was masked by statin use. Indeed, among HIV-infected non-statin users, the duration of known HIV infection was associated with diminished cerebral VR, independent of age, consistent with the possibility that the accumulation of immunologic and inflammatory consequences of chronic HIV infection over the long-term may drive the development of cerebral endothelial dysfunction in this population.

Statin use was consistently associated with higher cerebral VR among HIV-infected individuals. Among their pleiotropic effects, statins improve endothelial function by upregulating expression and activity of endothelial nitric oxide synthase resulting in increased bioavailability of nitric oxide.[34] In individuals with vascular risk factors, prior stroke and impaired cerebrovascular function, statin use may increase cerebral VR.[15,35] However, a statistically significant increase in cerebral VR among individuals with preserved cerebrovascular function was not found, which may explain the lack of an observed benefit of statin use on cerebral VR_{hyper} among uninfected controls in our study. The increase in cerebral VR demonstrated with statin use argues for a unique benefit of statins among HIV-infected individuals to prevent vascular events, which is being evaluated in an ongoing trial.

Although untreated hypertension, which stimulates cerebrovascular remodeling and endothelial damage,[36] has been linked to reduced cerebral VR in the general population, [37–40] we did not observe a statistically significant association between hypertension and lower cerebral VR in our cohort. This may be at least partially accounted for by near universal use of anti-hypertensive therapy among individuals with hypertension in our cohort. Diabetes mellitus, however, which alters endothelial function and has been correlated with diminished cerebral VR,[23,41] was associated with reduced cerebral VR among HIV-infected individuals. HIV-infected individuals are at high risk for diabetes mellitus,[42,43] an established risk factor for cerebral small vessel disease in the general population. Diabetes mellitus has been identified as a risk factor for worse neurocognitive performance in older HIV-infected individuals.[44,45] One hypothesis that merits further investigation is whether this association between diabetes mellitus and neurocognitive dysfunction is mediated through impaired cerebral microvascular function.

While heavy alcohol use is a strong independent risk factor for stroke,[46] moderate alcohol intake has been shown to be protective against ischemic stroke and associated with better systemic endothelial function[47,48] The majority of individuals who consumed alcohol in our study fell into the category of “moderate use,” defined as up to 2 drinks per day, which may explain the correlation with higher cerebral VR. We included methamphetamine in the forward stepwise selection process to account for differences in cerebral VR by HIV status due to discrepant methamphetamine use. However, its effect on cerebral VR should be interpreted cautiously given few methamphetamine users in the cohort.

Although age did not affect cerebral VR in our study, non-white race had a consistently negative impact on cerebral VR in both the full cohort and in the HIV-only model. Most studies of cerebral endothelial function have not evaluated differences in cerebral VR by race or ethnicity. Based on studies of systemic endothelial function, differences in vascular biology by race/ethnicity may result in more impaired endothelium-dependent and microvascular vasodilatory function in blacks compared with whites, independent of vascular and metabolic risk factors.[49,50] Although stroke incidence in the general population is strongly related to black race,[51] none of the large cohort studies of cerebrovascular events in HIV-infected individuals have demonstrated non-white race as a risk factor for either ischemic or hemorrhagic stroke.

Our study has several limitations that bear mention. First, this was a small, cross-sectional study, limiting our ability to prospectively assess changes in cerebral VR over time. Secondly, we lacked markers of systemic inflammation or immune activation obtained at the time of TCD with which to compare cerebrovascular function. Additionally, the overwhelming majority of our study participants were men, which reflects the general demographic make-up of the SCOPE cohort. Thus, we are not able to generalize our results to HIV-infected women. Given our data that the relative risk of stroke conferred by HIV infection in women is greater than men,[3,4] studies aimed specifically at evaluating cerebrovascular function in women should be a top priority. Furthermore, use of one technologist in a single vascular laboratory precluded us from assessing interrater agreement for cerebral VR, although data on interrater reliability of TCD-measured cerebral VR are available.[52] Lastly, there were differences at baseline between the HIV-infected cohort and the uninfected control group, which may have affected the association between HIV status and cerebral VR. However, the differences in cerebral VR observed by HIV status persisted even after adjusting for these baseline differences.

The findings from this study advance our current knowledge of the impact of treated, virally suppressed HIV infection on vascular dysfunction by extending its negative effect to the cerebral vasculature. Importantly, these results provide one possible mechanism to explain increased cerebrovascular risk in HIV-infected individuals. Future studies should compare longitudinal changes in cerebrovascular function between HIV-infected individuals and uninfected controls, in addition to correlating markers of immune activation and inflammation with cerebrovascular function in HIV infection. Assessment of cerebral VR has potential applications for use to identify individuals with cerebrovascular dysfunction at greater risk for stroke and to monitor response to interventions intended to reduce cerebrovascular risk in HIV infection.

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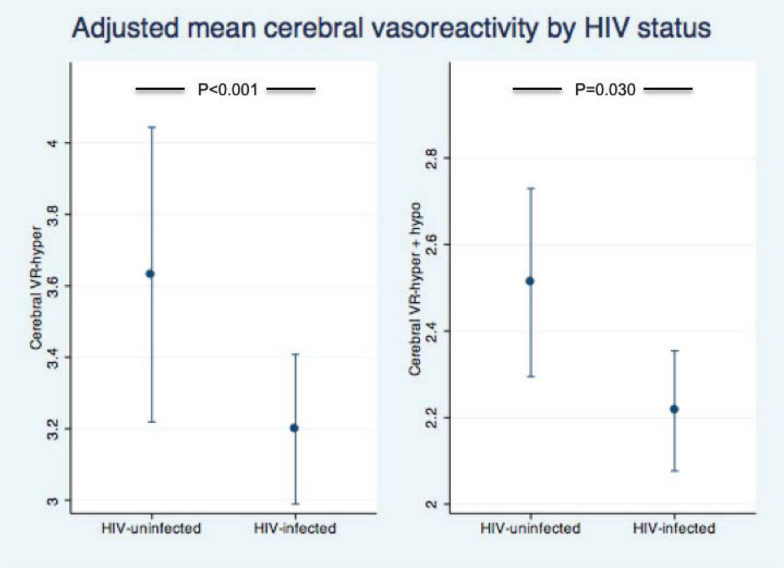

Figure 1.

Adjusted mean cerebral vasoreactivity and 95% confidence intervals (for non-statin users) by HIV status. Models adjusted for age, race, diabetes mellitus, hypertension, statin use, aspirin use, alcohol consumption, and methamphetamine use. *Cerebral VR-hyper*, cerebral vasoreactivity in response to hypercapnia; *cerebral VR-hyper + hypo***,** cerebral vasoreactivity in response to the full range of hyper- and hypocapnia.

Table 1

Demographic and clinical characteristics of treated, virally suppressed HIV-infected individuals and uninfected controls

	HIV-infected (n=65)	Uninfected controls (n=28)	P value
Demographics (% of total unless noted)			
Age (years), mean (SD)	57.2 (8.5)	53.5 (10.0)	0.071
Male sex	95	96	0.80
Non-white race/ethnicity	26	32	0.56
Vascular and other risk factors (% of total unless noted)			
Hypertension	49	29	0.065
Dyslipidemia	57	21	0.002
Statin use	48	11	0.001
Aspirin use	49	21	0.012
Coronary heart disease	5	0	0.55
Diabetes mellitus	12	0	0.10
Hepatitis C infection	23	4	0.033
Prior stroke	3	0	1.00
Migraines	11	18	0.50
Sleep apnea	15	4	0.16
Current substance use (% of total unless noted)			
Alcohol use	55	79	0.034
0 drinks per day	45	21	0.20
Up to 1 drink per day	40	61	
Up to 2 drinks per day	9	11	
Up to 3 drinks per day	6	7	
Tobacco use	14	25	0.19
Cocaine use	5	7	0.63
Heroin use	0	4	0.30
Methadone use	2	4	0.51
Methamphetamine use	6	4	1.00

	HIV-infected (n=65)	Uninfected controls (n=28)	P value
Marijuana use	48	21	0.018
HIV-specific factors			
CD4 count (cells/mm^3), mean (SD)	596 (251)	---	---
Nadir CD4 count (cells/mm^3), mean (SD)	242 (175)	---	---
Duration of HIV infection (years), mean (SD)	20.2 (6.8)	---	---
Duration of viral suppression (years),mean (SD)	7.8 (3.8)	---	---
Current ART regimen containing (%):		---	---
PI	42	---	---
Any NRTI	98	---	---
Abacavir	32	---	---
Any NNRTI	55	---	---
Integrase inhibitor	34	---	---
Maraviroc	5	---	---

ART, antiretroviral therapy; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor

Table 2

Bivariate and multivariate models of the effect of HIV infection and other risk factors on cerebral vasoreactivity in response to hypercapnia (cerebral VR_{hyper})

	HIV-infected (n=65) + HIV-uninfected (n=28), Total n=93 Total observations (left + right sides) n=175			
	Difference in mean cerebral VR_{hyper}[1] (95% CI)	**P value**	**Difference in mean cerebral VR_{hyper}[1] (95% CI)**	**P value**
	Bivariate analyses		**Multivariate model[4]**	
Demographics				
Age (per 10-year increase)	+0.03 (−0.20 to +0.26)	0.81	−0.08 (−0.29 to +0.13)	0.45
Male sex	−0.26 (−1.32 to 0.80)	0.63		
Race (non-white versus white)	−0.65 (−1.11 to −0.20)	0.005	−0.68 (−1.09 to −0.27)	0.001
Vascular and other risk factors				
Hypertension	−0.04 (−0.46 to +0.39)	0.86	−0.01 (−0.39 to +0.38)	0.97
Dyslipidemia	+0.14 (−0.28 to +0.56)	0.52		
Statin use	+0.12 (−0.32 to +0.56)	0.60	Statin use in HIV-infected[5] +0.51 (+0.06 to +0.96) Statin use in HIV-uninfected −0.65 (−1.73 to +0.42)	0.028 0.24
Aspirin use	+0.27 (−0.15 to +0.70)	0.21	+0.39 (−0.03 to +0.81)	0.067
Coronary heart disease	+0.03 (−1.16 to +1.22)	0.96	---	---
Diabetes mellitus	−0.88 (−1.62 to −0.15)	0.019	−0.91 (−1.60 to −0.23)	0.009
Hepatitis C infection	−0.51 (−1.06 to +0.05)	0.073	---	---
Prior stroke	+0.89 (−0.55 to +2.32)	0.23	---	---
Migraines	+0.27 (−0.35 to +0.90)	0.39	---	---
Sleep apnea	+0.21 (−0.44 to +0.86)	0.53	---	---
Traumatic brain injury	−0.09 (−0.89 to +0.71)	0.83	---	---
Substance use[2]				
Alcohol use (for each additional drink per day)	+0.22 (−0.03 to +0.48)	0.083	+0.26 (+0.03 to +0.48)	0.027
Tobacco use	−0.32 (−0.88 to +0.23)	0.26	---	---
Cocaine use	−0.69 (−1.62 to +0.24)	0.15	---	---
Heroin use	+0.48 (−1.56 to +2.51)	0.65	---	---

	HIV-infected (n=65) + HIV-uninfected (n=28), Total n=93 Total observations (left + right sides) n=175			
	Difference in mean cerebral VR_{hyper}[1] (95% CI)	**P value**	**Difference in mean cerebral VR_{hyper}[1] (95% CI)**	**P value**
	Bivariate analyses		**Multivariate model[4]**	
Methamphetamine use	−1.05 (−1.96 to −0.13)	0.025	−1.13 (−1.90 to −0.36)	0.004
Marijuana use	−0.001 (−0.43 to 0.43)	1.00	---	---
HIV and HIV-specific factors[3]				
HIV infection	−0.59 (−1.03 to −0.14)	0.010	−0.86 (−1.30 to −0.42)[6]	<0.001
CD4 count (per 50cells/mm^3 increase)	+0.001 (−0.05 to +0.05)	0.97	---	---
Nadir CD4 count (per 50cells/mm^3 increase)	+0.04 (−0.03 to +0.11)	0.27	---	---
Duration of HIV infection (per year)	−0.004 (−0.04 to +0.03)	0.83	---	---
Duration of viral suppression (per year)	+0.02 (−0.05 to +0.08)	0.66	---	---
Current ART regimen contains:				
PI	+0.14 (−0.38 to +0.65)	0.61		
Any NRTI	−1.20 (−3.25 to +0.85)	0.25	---	---
Abacavir	+0.19 (−0.36 to +0.73)	0.50		
Any NNRTI	+0.08 (−0.43 to +0.60)	0.75		
Integrase inhibitor	−0.24 (−0.78 to +0.30)	0.38		
Maraviroc	+0.63 (−0.58 to +1.83)	0.31		

[1] Expressed as percentage change in mean flow velocity per unit change in end-tidal carbon dioxide

[2] Current versus no current use unless otherwise noted

[3] Effect of HIV-specific factors on cerebral vasoreactivity among HIV-infected cohort only

[4] Model adjusted only for risk factors listed in the multivariate model column

[5] p value for interaction between HIV and statin use = 0.044

[6] In the multivariate model, the difference in mean cerebral vasoreactivity shown for HIV infection compared with no HIV infection is specifically for non-statin users

Table 3

Bivariate and multivariate models of the effect of HIV infection and other risk factors on cerebral vasoreactivity in response to hyper- and hypocapnia (cerebral $VR_{hyper+\ hypo}$)

	HIV-infected (n=65) + HIV-uninfected (n=28), Total n=93 Total observations (left + right sides) n=175			
	Difference in mean cerebral $VR_{hyper\ +\ hypo}$[1] (95% CI)	P value	Difference in mean cerebral $VR_{hyper\ +\ hypo}$[1] (95% CI)	P value
	Bivariate analyses		Multivariate model[4]	
Demographics				
Age (per 10-year increase)	+0.06 (−0.08 to +0.20)	0.40	−0.01 (−0.15 to +0.13)	0.88
Male sex	+0.13 (−0.51 to 0.77)	0.68	---	---
Race (non-white versus white)	−0.09 (−0.38 to +0.19)	0.53	−0.11 (−0.38 to +0.17)	0.44
Vascular and other risk factors				
Hypertension	−0.05 (−0.31 to +0.21)	0.73	−0.12 (−0.38 to +0.14)	0.36
Dyslipidemia	+0.19 (−0.06 to +0.45)	0.14	---	---
Statin use	+0.26 (−0.005 to +0.52)	0.054	+0.42 (+0.13 to +0.71)	0.004
Aspirin use	+0.15 (−0.11 to +0.41)	0.27	+0.14 (−0.13 to +0.42)	0.31
Coronary heart disease	−0.37 (−1.09 to +0.35)	0.32	---	---
Diabetes mellitus	−0.41 (−0.87 to +0.04)	0.072	−0.46 (−0.91 to −0.01)	0.047
Hepatitis C infection	−0.15 (−0.49 to +0.19)	0.40	---	---
Prior stroke	+0.39 (−0.49 to +1.27)	0.39	---	---
Migraines	+0.14 (−0.24 to +0.52)	0.48	---	---
Sleep apnea	−0.15 (−0.55 to +0.25)	0.45	---	---
Traumatic brain injury	+0.02 (−0.47 to +0.51)	0.94	---	---
Substance use[2]				
Alcohol use (for each additional drink per day)	+0.23 (+0.08 to +0.38)	0.003	+0.19 (+0.04 to +0.33)	0.012
Tobacco use	+0.16 (−0.18 to +0.50)	0.37	---	---
Cocaine use	−0.14 (−0.71 to +0.44)	0.64	---	---
Heroin use	+0.71 (−0.52 to +1.95)	0.26	---	---
Methamphetamine use	−0.33 (−0.90 to +0.24)	0.26	−0.31 (−0.83 to +0.20)	0.23

	HIV-infected (n=65) + HIV-uninfected (n=28), Total n=93 Total observations (left + right sides) n=175			
	Difference in mean cerebral $VR_{hyper + hypo}$[1] (95% CI)	**P value**	**Difference in mean cerebral $VR_{hyper + hypo}$[1] (95% CI)**	**P value**
	Bivariate analyses		**Multivariate model[4]**	
Marijuana use	+0.04 (−0.23 to +0.30)	0.78	---	---
HIV and HIV-specific factors[3]				
HIV infection	−0.20 (−0.48 to +0.07)	0.15	−0.30 (−0.56 to −0.03)	0.030
CD4 count (per 50cells/mm^3 increase)	+0.02 (−0.02 to +0.05)	0.34	---	---
Nadir CD4 count (per 50cells/mm^3 increase)	+0.01 (−0.03 to +0.06)	0.60	---	---
Duration of HIV infection (per year)	+0.007 (−0.02 to +0.03)	0.56	---	---
Duration of viral suppression (per year)	+0.03 (−0.02 to +0.07)	0.22	---	---
Current ART regimen contains:				
PI (yes/no)	−0.08 (−0.42 to +0.25)	0.62		
Any NRTI (yes/no)	−0.11 (−1.45 to +1.23)	0.87	---	---
Abacavir (yes/no)	+0.08 (−0.27 to +0.43)	0.65		
Any NNRTI (yes/no)	+0.08 (−0.25 to +0.41)	0.62		
Integrase inhibitor (yes/no)	−0.18 (−0.53 to +0.16)	0.30		
Maraviroc (yes/no)	+0.004 (−0.78 to +0.79)	0.99		

[1] Expressed as percentage change in mean flow velocity per unit change in end-tidal carbon dioxide

[2] Current versus no current use unless otherwise noted

[3] Effect of HIV-specific factors on cerebral vasoreactivity among HIV-infected cohort only

[4] Model adjusted only for risk factors listed in the multivariate model column

Table 4

Multivariate model[1] of the effect of risk factors on cerebral vasoreactivity in response to hypercapnia (cerebral VR_{hyper}) and to hyper- and hypocapnia (cerebral $VR_{hyper + hypo}$) among HIV-infected cohort only

	HIV-infected only (n=65)Total observations (left + right sides) n=122			
	Difference in mean cerebral VR_{hyper}[2] (95% CI)	**P value**	**Difference in mean cerebral $VR_{hyper + hypo}$[2] (95% CI)**	**P value**
Age (per 10-year increase)	−0.13 (−0.40 to +0.14)	0.35	+0.08 (−0.09 to +0.26)	0.36
Race (non-white versus white)	−0.88 (−1.40 to −0.35)	0.001	−0.23 (−0.59 to +0.12)	0.20
Diabetes mellitus	−0.92 (−1.60 to −0.24)	0.008	−0.53 (−1.00 to −0.07)	0.025
Statin use	+0.46 (+0.01 to +0.91)	0.046	+0.36 (+0.06 to +0.67)	0.019
Aspirin use	+0.44 (−0.03 to +0.92)	0.068	---	---
Alcohol use (for each additional drink per day)	+0.34 (+0.07 to +0.61)	0.013	+0.17 (−0.01 to +0.36)	0.070
Methamphetamine use (current versus no current use)	−1.12 (−1.99 to −0.25)	0.012	---	---
Duration of viral suppression (per year)	+0.05 (−0.004 to 0.11)	0.071	+0.04 (−0.001 to +0.08)	0.053
Most recent CD4 count > 500 cells/mm^3	---	---	+0.33 (+0.03 to +0.62)	0.032

[1] Models adjusted for risk factors listed in each respective column

[2] Expressed as percentage change in mean flow velocity per unit change in end-tidal carbon dioxide