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The Regional Pattern of Abnormal Cerebrovascular Reactivity in HIV-Infected, Virally Suppressed Women

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Abstract

Objective—The purpose of this study was to assess whole brain and regional patterns of cerebrovascular reactivity (CVR) abnormalities in HIV-infected women using quantitative whole brain arterial spin labeling (ASL). We hypothesized that HIV-infected women would demonstrate decreased regional brain CVR despite viral suppression.

Design—This cross sectional study recruited subjects from the Bay Area Women's Interagency Health Study (WIHS) - a cohort study designed to investigate the progression of HIV disease in women. In addition to conventional noncontrast cerebral MRI sequences, perfusion imaging was performed before and after the administration of intravenous acetazolamide.

Methods—CVR was measured by comparing quantitative ASL brain perfusion before and after administration of intravenous acetazolamide. In order to validate and corroborate ASL-based whole brain and regional perfusion, phase-contrast (PC) imaging was also performed through the major neck vessels. FLAIR and susceptibility weighted sequences were performed to assess for white matter injury and microbleeds, respectively.

Results—Ten HIV infected women and seven uninfected, age-matched controls were evaluated. Significant group differences were present in whole brain and regional CVR between HIV infected and uninfected women. These regional differences were significant in the frontal lobe and basal ganglia. CVR measurements were not significantly impacted by the degree of white matter signal abnormality or presence of microbleeds.

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Conclusions—Despite complete viral suppression, dysfunction of the neurovascular unit persists in the HIV population. Given the lack of association between CVR and traditional imaging markers of small vessel disease, CVR quantification may provide an early biomarker of pre-morbid vascular disease.

Introduction

The increasing availability of antiretroviral therapies (ART) has altered the phenotype of HIV infection to a chronic, treatable disease. Despite viral suppression and immune reconstitution, individuals with HIV face increased rates of stroke and neurocognitive impairment compared with the general population [1,2]. The association of HIV and stroke has been most strongly observed in women living with HIV, who may have up to 75% greater risk of ischemic stroke than uninfected women [1]. Data from the Partners HIV cohort demonstrated that women with HIV have nearly two times the adjusted hazard for ischemic stroke compared with uninfected individuals, whereas men did not demonstrate any significant difference in risk of stroke by HIV status. Accelerated atherosclerosis, increased inflammation, and endothelial dysfunction have been observed in HIV infected, virally suppressed populations, and these factors have been proposed to correlate with the increased incidence of both neurovascular and cardiovascular disease [3,4]. Moreover, cerebrovascular disease has been suggested to be a key contributor to HIV-associated Neurocognitive Disorder (HAND) [5–11]. The etiology of HAND remains incompletely defined but is likely multifactorial: reflecting the effects of viral infection, immunologic response, medication usage, and comorbidities.

Endothelial and neurovascular unit (NVU) dysfunction have been shown to be highly correlated to HAND [12–14]. The NVU, consisting of endothelial cells, pericytes, astrocytes, and microglia, is the principal regulator of the blood-brain-barrier (BBB) and cerebrovascular reserve. The NVU active functional ability can be assessed by measuring cerebrovascular vasoreactivity (CVR), by which resting cerebral blood flow (CBF) is first measured, a vasoactive stimulus is then administered, and the resultant change in CBF is quantified.

Both oxygen and glucose are delivered to neurons by CBF via a coordinated action of interconnected blood vessels. In this way, brain function depends on the health of blood vessels and the cardiovascular system. The mammalian brain has evolved a unique mechanism for regional CBF control known as neurovascular coupling, the tight interaction between CBF and neuronal activity. Neurovascular dysfunction or uncoupling -- often seen as regional reductions in cerebral blood flow --has been shown to be a feature of neurodegenerative disease [15]. In addition, HIV infected virally-suppressed individuals have been shown to demonstrate resting neurovascular uncoupling, evidenced by resting CBF abnormalities as well as impaired whole brain CVR measured via transcranial doppler [16,17].

We characterized whole brain and regional patterns of CVR abnormalities in HIV-infected women using arterial spin labeling (ASL) MRI: a non contrast quantitative perfusion technique by which inflowing blood to the brain is magnetically labeled in order to assess

perfusion. We characterized whole brain and regional patterns of CVR abnormalities in a subset of the WIHS population using ASL MRI. We hypothesized that HIV-infected women would demonstrate decreased regional brain CVR despite viral suppression. Furthermore, we sought to estimate the strength of the relationships between resting cerebral blood flow, MRI-markers of cerebrovascular disease (e.g. white matter hyperintensities, microbleeds, cerebral hemorrhage, cortical stroke), traditional vascular risk factors, HIV laboratory biomarkers, and cognition.

Materials and Methods

Participants

We recruited participants with and without HIV from the Bay Area Women's Interagency Health Study (WIHS). WIHS is a large, comprehensive prospective cohort study designed to investigate the progression of HIV disease in women, and includes a group of HIV-negative, age matched controls. This population represents a unique and critical means of vascular effects of HIV in women. Accordingly, prior work from our group has both shown a substantial prevalence cardiovascular risk factors in this population, and an increased risk of stroke in women compared to men [1]. Controls and subjects represented a convenience sample of the WIHS proportion, representing subjects who were willing to return for our imaging protocol. Enrollment criteria for WIHS have been extensively published [18]. For this imaging substudy, all participants had to be at least 40 years of age, on continuous ART for at least 12 months with no change in the regimen 12 weeks prior to the study visit, and have an HIV RNA level below 75 copies for 24 weeks prior to the study visit. In addition, participants had to have documented cardiovascular disease or at least one cardiovascular risk factor (e.g., hypertension, dyslipidemia, diabetes mellitus, tobacco use, family history of cardiovascular disease). Vascular risk factors and neurocognitive testing data were captured during clinical research visits. Participants with and without HIV were similar in age, prevalence of cardiovascular risk factors and neurocognitive impairment (Table 1).

CVR Testing

In order to measure CVR, brain perfusion imaging was performed before and after administration of intravenous acetazolamide. Through its inhibition of carbonic anhydrase, acetazolamide lowers blood pH, leading to a predictable increase in CBF in normal healthy adults [19]. 1 gram acetazolamide was administered intravenously over 5 minutes, and perfusion imaging sequences were repeated. The CVR index was calculated, defined as the percentage increase in cerebral blood flow after the acetazolamide stimulus [19]. Post-stimulus perfusion maps were corrected for alterations in tagging efficiency using a previously validated phase-contrast technique [20,21].

Image Acquisition and Parameters

All imaging was performed on a 3T MR machine from a single vendor (General Electric 3T Discovery). Acquisition of brain CBF (perfusion) maps and processing was performed using an extensively described pipeline [22,23]. Briefly, perfusion-weighted images were computed by taking the difference between the mean-tagged and the mean-untagged ASL images. The first untagged ASL image (providing a full relaxed MR imaging signal) was

used as a reference image of the water density, used to calibrate the ASL signal for computing CBF, and used to estimate the transformation to coregister ASL and structural MR imaging. To accomplish registration between CBF and structural MR imaging maps, we augmented linear transformation, with 9 degrees of freedom, based on normalized mutual information by a nonlinear registration approach based on total variance [24].

The scaled distortion-corrected coregistered and partial volume -corrected perfusion-weighted images were normalized to the reference image to express the ASL signal in physical units of arterial water density as CBF (milliliters/100 g/minute).

The analysis aimed to measure blood flow in primarily grey matter tissue. To correct for partial grey/white matter volume effects, the scaled perfusion weighted image intensities were adjusted according to a linear model of grey and white matter contributions to the ASL signal and based on probabilistic segmentation of grey and white matter densities in each MRI voxel. Adjustments were made assuming a constant ratio between grey matter and white matter perfusion (2.5 times greater in grey matter) and the scaled reference image was adjusted assuming constant ratios between grey matter and water (0.78), white matter and water (0.65), and CSF and water (0.97) [17,22,23].

Structural MR imaging was also acquired using a T1-weighted 3D BRAVO sequence with the following acquisition parameters: TR: 7.424 ms, TE: 2.756 ms, flip angle 9°, FOV 256 mm, and resolution 1.0 x 1.0 x 1.0 mm. FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) was used to generate anatomic regions of interest statistics for CBF and volume. Fifty-eight brain regions from the left and right hemispheres derived from the Harvard-Oxford atlas were used in the analysis [25].

In order to validate and corroborate ASL-based whole brain and regional perfusion, phase-contrast (PC) imaging was also performed. PC images were acquired at a level in the neck just superior to the carotid bifurcation to include the bilateral internal carotid and vertebral arteries. The PC scan was acquired with the following acquisition parameters: repetition time: 15 ms, pixel size: 0.8 x 0.8 mm2, VENC: 100, echo time 4.276 seconds, slice thickness 4 mm, number of averages = 1.

Additional imaging sequences obtained included 2D FLAIR (TR: 11500 ms, TE: 88.8 ms, inversion time 2682.85 ms, FOV 512 mm, thickness 2.8 mm), SWAN (TR: 44.8 ms, TE: 25.148 ms, FOV 512 mm, thickness 4 mm), and DWI (TR: 9395 ms, TE: 74.3 ms, FOV 256 mm, thickness 2 mm). Time of flight angiography through the neck was performed in order to prescribe the phase contrast imaging plane perpendicular to the vascular geometry (TR: 25 ms, TE: 3.4 ms, FOV 512 mm, thickness 1.6 mm).

Analysis of Prior Cerebrovascular Injury and Small Vessel Ischemic Disease

Quantification of the degree of white matter hyperintensities was performed on FLAIR images by a neuroradiologist blinded to HIV status according to the Modified Fazekas scale, where grade 1 was defined by punctate lesions in the deep white matter with a maximum diameter of 9 mm for a single lesion and of 20 mm for grouped lesions, grade 2 was defined by early confluent lesions of 10–20 mm single lesions and ≥20 mm grouped lesions in any

diameter, and grade 3 was defined by single lesions or confluent areas of hyperintensity of >20 mm in diameter [26]. Foci of microhemorrhage were counted individually on the susceptibility weighted sequence and recorded. Evidence of prior macroscopic hemorrhage or cortical infarction were detailed during neuroradiologic assessment.

Assessment for the Presence of Neurocognitive Impairment

Neurocognitive testing data were captured during clinical research visits and interpreted by a neurologist according to the widely used classification schema of HIV-associated neurocognitive impairment known as the Frascati criteria [27]. Assessment was made on a four point scale, where 0 = within normal limits, 1 = asymptomatic neurocognitive impairment, 2= mild neurocognitive impairment, 3 = HIV associated dementia.

Statistical Analysis

Differences between HIV infected and uninfected groups were evaluated using the non-parametric Wilcoxin-Mann-Whitney test. These included resting and post-stimulus CBF measured by both ASL and PC as well as CVR within supratentorial cerebral lobes.

Linear mixed effects multivariate models were used to determine the factors that were significantly associated with regional resting CBF and regional CVR values in all participants; these factors included age, clinical vascular risk factors (dichotomized as either present or absent), HIV status, white matter intensity score, resting CBF, and microbleed score. Significant factors were identified using a stepwise model selection approach, where factors that had P less than 0.1 were included. All models included HIV serostatus and age.

In order to evaluate the spatial variance of regional CVR between the HIV+ and HIV- groups, we used covariance of variation (CoV) [20]. In order to compare the effect of HIV on lobar CVR, we compared effect sizes using Cohen's d [28].

In order to evaluate the factors significantly associated with severe burden of white matter intensities, the Modified Fazekas score was dichotomized and logistic regression was used to identify significant predictors using the same stepwise procedure.

Separate sensitivity analyses were performed to evaluate for the probability of confounding variables as well as the impact of influential participants/outliers [29]. Statistical significance was set at P less than 0.05 (two-sided) for all models. All statistical analyses were performed using the programming language R using R 3.5.3.

Results

Participants

Ten HIV infected women and seven uninfected, age-matched women were included in these analyses. Across all participants, age ranged from 42 to 76 years. Cardiovascular and cerebrovascular risk factors were present within the HIV+ groups in proportions similar to those in the HIV- group (Table 1). The HIV+ and HIV- groups included two and one participants, respectively, with moderate cognitive impairment.

Factors predictive of resting CBF and CVR

Mean whole brain resting CBF, measured from phase-contrast, in HIV+ individuals was 581 ml/min, SD = 83; while mean resting CBF in HIV- individuals was 597 ml/min, SD = 176. The mean resting CBF across all considered regions of interest, measured from ASL, in HIV + was 45.1 ml/min/100g, SD = 11.3; while HIV- mean = 49.6 ml/min/100g, SD = 9.84. No statistically significant differences in resting whole brain CBF (phase-contrast) or regional CBF (ASL) between HIV+ vs. HIV- individuals were found.

Optimal linear multivariate models that predicted resting CBF included age ($B = 12.1$, $P < .001$) and high white matter hyperintensity score (fazekas 3, $B = 40.8$, $P < .001$). HIV status (P = .3), vascular risk factors (P = .8) and microbleeds (P = .6) were not significant predictors of resting CBF.

Administration of acetazolamide produced significant differences in whole brain and regional CBF (p<.001) in all participants (Figure 1, Table 2). Mean post-stimulus whole brain CBF in HIV+ was 953 ml/min, SD = 117; while the mean post stimulus CBF in HIV- was 1014 ml/min, SD = 236. Regional cerebral blood flow varied among different ROIs with HIV+ mean being 73.2 ml/min/100g, SD = 17.4; HIV- mean was 86.5 ml/min/100g, SD = 27.9. Significant differences ($P < .001$) were found in both regional and whole brain post-stimulus vasoactive CBF for HIV+ compared with HIV- individuals.

Factors predictive of cerebral vasoreactivity

HIV- individuals demonstrated greater spatial variance in CVR (CoV = .28) vs. HIV+ (CoV = 17). The optimal linear model demonstrated that the significant predictors of regional CVR included HIV status as well as pre-stimulus CBF (Figure 2). HIV+ status ($B = -1.3$, $P < .01$) predicted reduced regional CVR, whereas age, vascular risk factors, vascular white matter hyperintensities or microbleeds did not. Pre-stimulus whole brain CBF had a very small effect ($B = .001$, $P = .04$).

Lobar/regional CVR significantly differed between HIV+ and HIV- (Figure 3). These differences were significant in the frontal lobe ($d = .7$, $P = .003$), and basal ganglia ($d = .6$, $P = .02$).

Temporal volumes showed small effect size without significance ($d = .3$, $P = .2$). Occipital and parietal volumes showed negligible effects.

Factors predictive of burden of cerebral small vessel disease

White matter hyperintensities, chronic microbleeds, acute hemorrhage, and acute strokes were measured between infected and uninfected groups. No patient had an acute stroke or acute hemorrhage. No uninfected patients had chronic microbleeds, whereas two infected patients had chronic microbleeds. 4/7 (57%) uninfected patients had some degree of white matter signal abnormality, compared with 6/10 (60%) infected patients.

Logistic regression was performed to evaluate factors associated with high probability of severe white matter intensity scores; however, neither age, HIV status, vascular risk factors, or microbleed score reached significance.

Sensitivity Analysis

The model for prediction of regional CVR demonstrated robustness to the presence of bias. We calculated the percent bias necessary to invalidate the inference; to invalidate an inference, 56% of the estimate would have to be due to bias. This is based on a threshold of −0.024 for statistical significance ($\alpha = 0.05$) [29]. To invalidate the significance of the model, 8 HIV+ subjects would have to be replaced with HIV- controls.

To evaluate the effect of including 2 HIV+ with HAND (MND), we removed these individuals from the analysis and re-evaluated the model. Removal of these individuals had no effect on the significance of main predictors. However, this model demonstrated significance ($P = .001$) for an interaction between HIV and pre-stimulus CBF, albeit without a meaningful coefficient ($B = .006$). Spatial variance minimally decreased after removing these individuals (CoV = .14).

Discussion

Our study demonstrated that there are significant group differences in whole brain and regional CVR between HIV infected and uninfected women. These regional differences were significant in the frontal lobe and basal ganglia. These results corroborate findings from prior work investigating CVR using transcranial doppler response to hypercapnia in HIV+ individuals [16]. Moreover, our findings add new data to a growing literature detailing cerebrovascular abnormalities in treated HIV+ populations [13,14,30]. Importantly, these data also underscore the ability of MRI-based CVR measurements to evaluate regional differences in endothelial dysfunction.

Recent work by Chaganti et al. demonstrated increased capillary permeability in similar regions, including anterior frontal white matter and the basal ganglia in HIV infected individuals compared with controls, using dynamic contrast enhanced perfusion MRI [31]. This increased permeability reflects pathology of the NVU which dovetails with the impaired CVR in the same regions in our study. In addition, Nichols et al. demonstrated relative inferior frontal and ganglionic atrophy in HIV positive, virally suppressed individuals, and Cysique et al. demonstrated evidence of chronic inflammation in the frontal white matter and basal ganglia using MR spectroscopy [32,33]. Taken together, these data suggest frontal and ganglionic cerebrovascular changes in the HIV+ brain appear to mirror topographies of volume loss, in keeping with prior observations from multiple prior studies [34]. Prior pathologic and genomic work has demonstrated strong evidence supporting a direct link between HIV and endothelial dysfunction. Gelman et al. describe abnormal transcription regulation in brain genes expressed by endothelial cells in HIV infected, virally suppressed individuals [2]. Furthermore, biomarkers related to endothelial dysfunction have been shown to be elevated in individuals with HIV [14]. Moreover, we here detail a neuroimaging technique which may provide a useful link in future studies between laboratory biomarkers of endothelial dysfunction and the spatial distribution of brain abnormalities.

Interestingly, HIV- individuals demonstrated greater spatial variance in CVR. Prior work has shown spatial variance in CBF is associated with decreased velocities within the cervical

vasculature which often accompanies aging [20]. However, in the current dataset, no group differences in basal flow and velocities in the neck were found. Spatial heterogeneity may reflect heterogeneity in the control population on the basis of unknown or unmeasured factors, or simply be due to chance, reflecting the relatively small sample size of this pilot study.

CVR measurements were not significantly impacted by the degree of white matter signal abnormality or presence of microbleeds. These imaging features have traditionally been considered markers of small vessel disease and aging [35–37], but the relationship between small vessel disease and HIV is still unresolved [3,6,10,11]. The overlapping risk factor burden between vascular risk factors, cognitive impairment, HIV disease progression and HAND despite ART is well known [13,38]. The lack of a relationship between traditional clinical vascular risk factors, neuroimaging metrics, and CVR measurements in our study suggest that impaired CVR may reflect a feature of vascular pathology which would otherwise not be captured within conventional neuroimaging datasets. Similarly, the lack of significant group differences in resting CBF and the lack of impact of resting CBF in predicting CVR, suggests that CVR testing may be a useful biomarker of pre-morbid or early endothelial impairment. In the current data, sensitivity analyses show that the impact of HIV on CVR does not depend on the few cognitively impaired individuals within our small cohort. When cognitively impaired patients are removed from the model, the significant impact of HIV on regional CVR persists.

While the presence of HAND in the ART era suggests a persistent effect of HIV infection in the central nervous system, the exact pathophysiology of this relationship is not entirely understood. Given the complex nature of HIV associated comorbidities and risk factors, long-term and large studies are needed to assess cerebrovascular disease, vascular cognitive impairment, and mild HAND phenotypes optimally. MRI-based CVR testing represents a new and potentially more sensitive assessment of endothelial function, and in turn, could be incorporated into ongoing neuroimaging and laboratory biomarker studies evaluating the complex clinical phenotype of HAND.

There were no significant differences in whole brain or regional resting (pre-acetazolamide) perfusion between the two study groups. Prior work has demonstrated altered resting cerebral perfusion in HIV+ individuals when compared with healthy individuals and those with neurocognitive impairment [17]. This difference may be explained by the larger effect size of CVR testing when compared with CBF abnormalities, in conjunction with our relatively smaller study population. In addition, our study population contained only women, were of a younger mean age, and contained disproportionately fewer subjects with cognitive impairment.

The results of our study should be interpreted along with its limitations. As this study was limited by a relatively small sample size, and only included women, our findings are preliminary and need to be verified in a larger, more inclusive, independent study. Additionally, the age of HIV+ participants reflects seroconversion before the introduction of combination ART, and this finding may not be generalizable to younger post-ART populations.

Conclusion

The post-ART era has altered the neuropathology of HIV infection. Despite complete viral suppression, dysfunction of the neurovascular unit persists in the HIV population. Future work should include longitudinal followup of these patients to identify if identifiable abnormalities in CVR precede neurovascular and/or neurocognitive compromise. Given the lack of association between CVR and traditional imaging markers of small vessel disease, CVR quantification may provide an early biomarker of pre-morbid vascular disease, and allow for novel treatment strategies for these patients in this era of chronic, virally suppressed, HIV infection.

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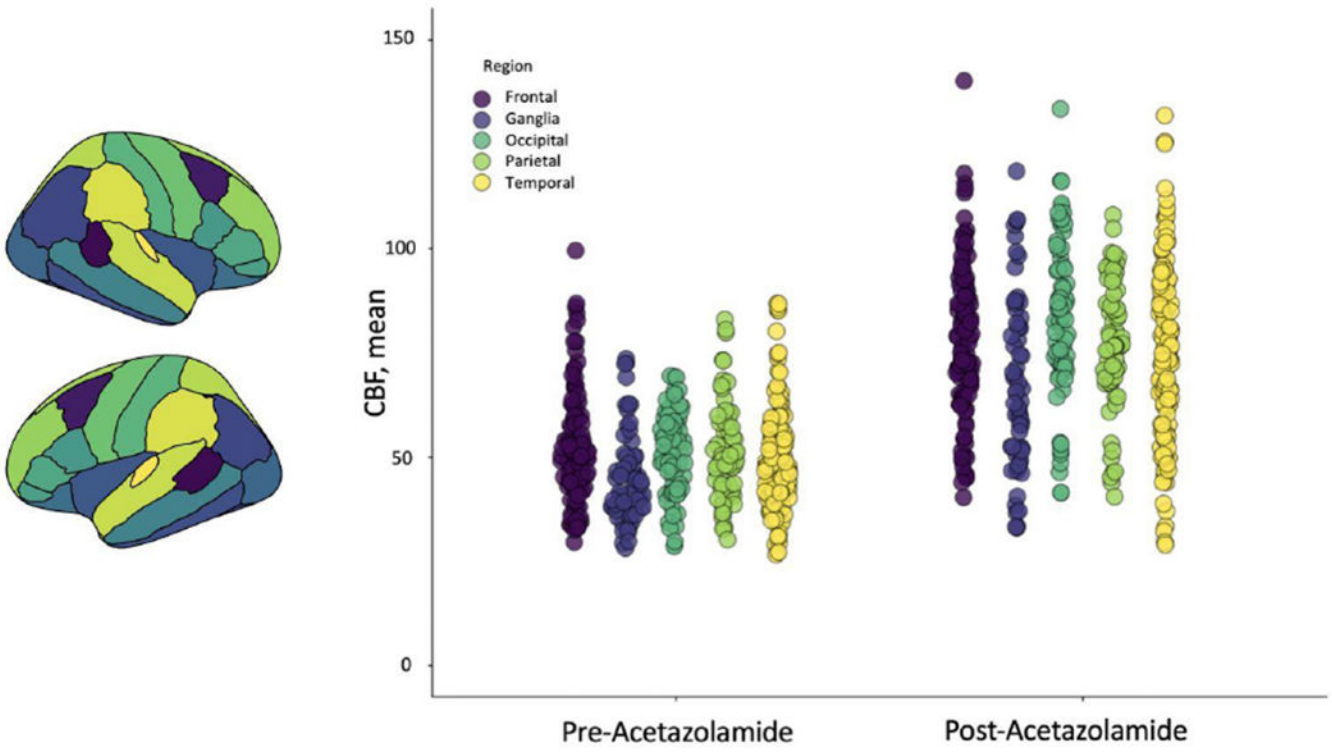

Figure 1:

Administration of acetazolamide produced significant differences in whole brain and regional CBF (P<.001) in all participants. ROIs measured from ASL demonstrate significant increases in regional CBF after the administration of acetazolamide.

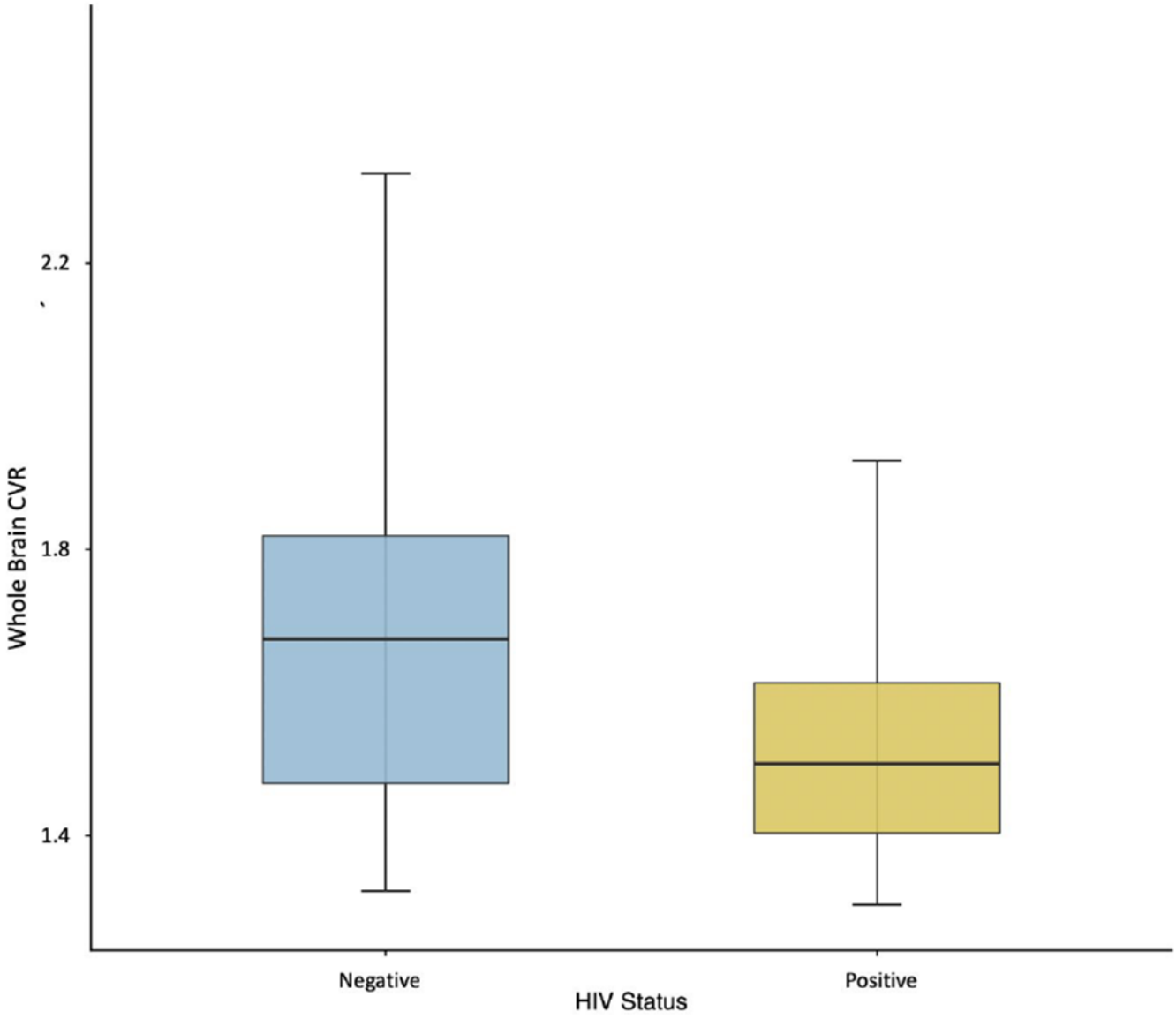

Figure 2:
HIV- individuals demonstrated greater mean regional CVR compared to HIV+ individuals (P<.01).

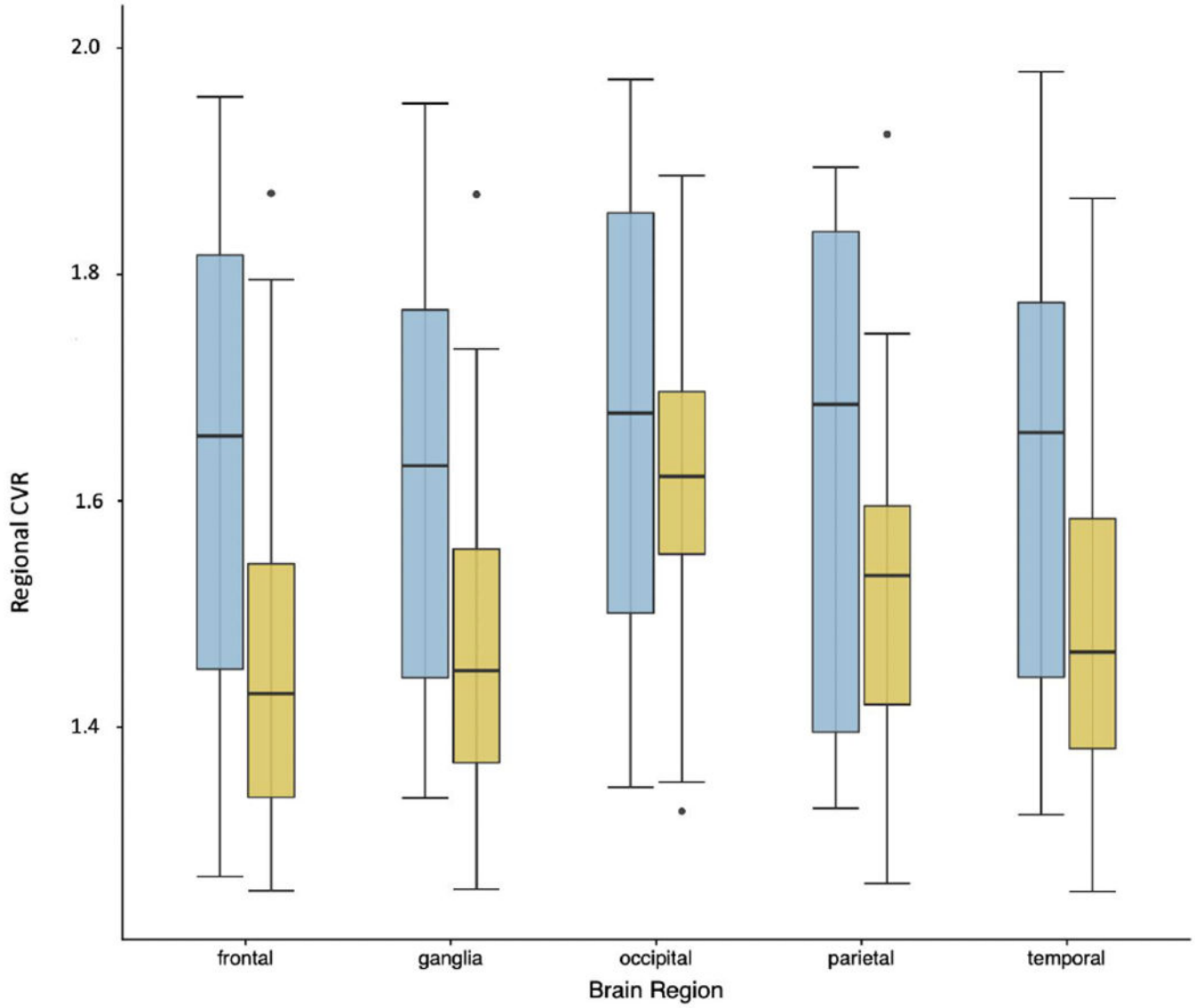

Figure 3:
Lobar CVR significantly differed between HIV+ and HIV- subjects in frontal and basal ganglia regions (P<.02).

Table 1

Demographic, comorbidity, neurocognitive, and CD4 data of HIV positive and HIV negative subjects

Covariate	HIV+	HIV-
Age (mean, SD)	56.7, 11.0	55.6, 5.0
Ethnicity	5/10 African American (non hispanic) 3/10 White (non hispanic) 1/10 White (hispanic) 1/10 Other	6/7 African American (non hispanic) 1/7 White (non hispanic)
Tobacco	2/10	2/7
Hypertension	5/10	5/7
Diabetes	0/10	1/7
Neurocognitively Impaired	2/10	1/7
CD4 Nadir (mean, SD)	272.6, 195.0	1175.4, 482.4

Table 2

Pre and post-acetazolamide cerebral blood flow for HIV positive and HIV negative subjects

HIV status	Region	Basal CBF (mean)	SD	ACZ-CBF (mean)	SD
Negative	Frontal	**49.51**	10.03	**99.19**	39.01
Negative	Ganglia	**44.6**	8.06	**83.8**	20.81
Negative	Occipital	**50.12**	10.45	**102.94**	32.34
Negative	Parietal	**50.86**	11.89	**87.19**	19.15
Negative	Temporal	**49.14**	11.06	**93.29**	24.8
Positive	Frontal	**48.14**	12.72	**73.59**	16.7
Positive	Ganglia	**42.12**	10.59	**65.51**	16.61
Positive	Occipital	**43.02**	8.3	**80.05**	14.72
Positive	Parietal	**46.05**	11.34	**77.24**	15.07
Positive	Temporal	**45.25**	12.12	**72.6**	18.39