Cerebrovascular Contributions to Neurocognitive Disorders in People Living With HIV

Jose Gutierrez, MP, MPH,[a,b] Tiffany N. Porras, MPH,[c] Moka Yoo-Jeong, BS,[d] Farid Khasiyev, MD,[e] Kay C. Igwe, BS,[a] Krystal K. Laing, BS,[a] Adam M. Brickman, PhD,[a,b,f] Marykay Pavol, PhD,[a] and Rebecca Schnall, RN, PhD[g,h]

Background: To investigate a comprehensive array of magnetic resonance imaging (MRI)-based biomarkers of cerebrovascular disease (CVD) in a cohort of people living with HIV (PLWH) and relate these imaging biomarkers to cognition.

Settings: Cross-sectional, community-based study.

Methods: Participants were PLWH in New York City, aged 50 years or older. They underwent a brain magnetic resonance angiography or MRI to ascertain 7 MRI markers of CVD: silent brain infarcts, dilated perivascular spaces, microhemorrhages, white matter hyperintensity volume, white matter fractional anisotropy and mean diffusivity (measures of white matter integrity), and intracranial large artery stenosis. Participants underwent a battery of neurocognitive tests to obtain individual and global cognitive scores representative of various aspects of cognition.

Results: We included 85 participants (mean age 60 ± 6 years, 48% men, 78% non-Hispanic Black), most of them with well-controlled HIV (75% with CD4 cell count > 200 cells/mm^3 and viral load < 400 copies/mL at or near the time of the MRI scan). Silent brain infarcts, intracranial large artery stenosis, and poor white matter integrity were associated with poorer performance in at least one cognitive domain, but the sum of these 3 MRI markers of CVD was associated with lower working memory (B = −0.213, P = 0.028), list learning (B = −0.275, P = 0.019), and global cognition (B = −0.129, P = 0.007).

Conclusions: We identified silent brain infarcts, intracranial large artery stenosis, and poor white matter integrity as exposures that may be modifiable and may, therefore, influence cognitive decline. In addition, these MRI markers of CVD may help in identifying PLWH at higher risk of cognitive decline, which may be more amenable to targeted therapies.

Key Words: HIV, HAND, cognition, silent brain infarcts, intracranial stenosis, dementia

(*J Acquir Immune Defic Syndr* 2021;88:79–85)

INTRODUCTION

With the advent of combined antiretroviral therapy, people living with HIV (PLWH) are living longer. Yet the aging of the HIV population parallels a rise of dementia in this population.[1,2] Differentiating dementia and other HIV-associated neurocognitive disorders (HAND) has not been well achieved in PLWH. For example, there is evidence that in PLWH with persistent immunosuppression due to HIV or PLWH who have had an AIDS diagnosis, HAND may be explained by direct brain damage from opportunistic infections, neoplasia, or stroke.[3–6] On the other hand, direct central nervous system infection by HIV seems directly related to central nervous system inflammation[7,8] and has been associated with HAND even with well-controlled HIV infection,[9,10] suggesting that further investigation is warranted to understand the relationship between neurodegenerative disease and HIV.

In addition to neurodegenerative disease, PLWH are at a higher risk of cerebrovascular disease (CVD), overt (eg stroke) or covert (also known as silent or with no distinct symptoms). CVD is an important consideration in the context of neurodegenerative disease because in non–HIV-infected individuals, it is associated with a higher risk of dementia and poorer cognition. For example, people with intracranial large artery stenosis are at higher risk of dementia.[11–13] Similarly, silent brain infarcts and white matter hyperintensities (WMHs) are markers of CVD and have been associated with dementia, poorer cognition, and neurodegeneration.[14,15] People with stroke are at higher risk of dementia,[16] and those with dementia are at higher risk of stroke.[17] The mechanisms by which CVD contributes to dementia warrant further investigation. In fact, CVD may contribute to HAND, and markers of covert magnetic resonance imaging (MRI)-based CVD have been associated with HAND in PLWH.[18,19]

Received for publication December 6, 2020; accepted April 7, 2021.
From the [a]Department of Neurology, Columbia University Irving Medical Center, New York, NY; [b]Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY; [c]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [d]School of Nursing, Bouvé College of Health Sciences, Northeastern University, Boston, MA; [e]Department of Neurology, Saint Louis University, Saint Louis, MI; [f]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Columbia University Irving Medical Center, New York, NY; [g]School of Nursing, Columbia University Irving Medical Center, New York, NY; and [h]Department of Population and Family Health, Mailman School of Public Health, Columbia University Irving Medical Center, New York, NY.
Supported by NIH K24NR018621, Project 02 NR015737, AG R01057709.
The authors have no conflicts of interest to disclose.
Correspondence to: Jose Gutierrez, MD, MPH, Florence Irving Assistant Professor of Neurology, Columbia University Irving Medical Center, 710 W 168th Street, 6th Floor, Suite 639, New York, NY 10032 (e-mail: jg3233@cumc.columbia.edu).

Most studies on the vascular contributions to HAND have not included brain arterial imaging. Because brain large artery disease, specifically intracranial large artery stenosis, is an important predictor of stroke and cognition in people without HIV, we hypothesize that intracranial large artery stenosis may contribute to HAND in addition to other covert MRI-based biomarkers of CVD. The purpose of this study was to investigate a comprehensive array of covert MRI-based biomarkers of CVD in a cohort of PLWH and relate them to cognitive performance.

METHODS

Sample Description

Recruitment for the study began in January 2019 and ended in July 2019. Participants were recruited from a registry of individuals who had participated in previous studies and consented to be contacted for future studies and through study flyers posted at HIV-related community-based organizations in New York City. Snowball sampling was also used because enrolled participants shared flyers with their peers. Inclusion criteria for the study participants were as follows: (1) aged 50 years or older; (2) having an HIV/AIDS diagnosis; (3) taking antiretroviral therapy; (4) able to communicate and read in English; (5) comfortable using a tablet to complete a survey; (6) able to undergo an MRI safely; and (7) with a total error score of 20 or less on the short orientation memory concentration test (to evaluate capacity to consent). Participants were excluded if they were pregnant, provided ineligible responses pertaining to the MRI criteria, or scored greater than 20 on the short orientation memory concentration test. All research activities were reviewed and approved by the Columbia University Irving Medical Center Institutional Review Board. Demographic data such as age, sex, and race or ethnicity were self-reported. Vascular risk factors were identified by a combination of self-report and evidence of medication use to treat a given risk factor. History of CD4 cell counts and viral load near the time of visit were self-reported or extracted from the local medical records for those participants who followed up their care at our institution.

Procedures

Eligible participants provided written informed consent at their initial in-person visit. Each participant attended 2 visits; the first one included a neuropsychological assessment, a blood draw, and a demographic survey, and the second visit included an MRI scan.

Neuropsychological Assessment, Survey Assessment Measures, and Biological Specimens

A combination of neuropsychological tests were put together at the guidance of a neuropsychologist (M.P.) to thoroughly assess mental status, verbal intelligence, attention, recall, processing speed, language, memory, depression symptoms, and adaptive function. The tests were administered in the following order: Craft Story 21 Recall, the Benson Complex Figure Copy, Number Span Test—: Forward, Number Span Test—: Backward, Category Fluency (animals and vegetables), Trail Making Test (parts A and B), Craft Story Recall, the Benson Complex Figure—Recall/Recognition, Multilingual Naming Test, Verbal Fluency (C, F, and L), the Buschke Selective Reminding Test—Learning Trials, Grooved PegBoard test, Oral Trail Making Test (parts A and B), Neuro-QOL Depression Questionnaire, WHODAS 2.0 short form, the Buschke Selective Reminding Test—Delayed Recall/Recognition, NIH Toolbox Flanker Test, NIH Toolbox Pattern Comparison Test, NIH Toolbox Sorting Working Memory Task, Wide Range Achievement Test (WRAT—fourth edition)—Word Reading, and the Montreal Cognitive Assessment. Once participants completed the neuropsychological testing, they completed a demographic survey on an iPad.

Magnetic Resonance Imaging

MRI scans were obtained using a 3T scanner (Siemens MAGNETOM Prisma, Erlangen, Germany) with a 64-channel coil at the Columbia University Zuckerman Institute. The MRI scans were then administered by a certified MRI technologist who conducted the following sequences: 3DT1 magnetization prepared-rapid gradient echo [voxel size $1 \times 1 \times 1$ mm, isometric, repetition time/echo time (TR/TE) (ms) 2300/2.26, field of view 256 mm, and echo spacing 6.8 ms]; T2-weighted fluid-attenuated inversion recovery (FLAIR) [voxel size $0.45 \times 0.45 \times 0.90$ mm, TR/TE (ms) 5000/387, field of view 230 mm, and echo spacing 3.62 ms]; seceptibiliy weighted imaging (voxel size $0.86 \times 0.86 \times 1.50$ mm, TR/TE 27/20, flip angle 15 degrees, and field of view 220 mm); magnetic resonance angiography (MRA) time of flight [voxel size $0.26 \times 0.26 \times 0.5$ mm, TR/TE (ms) 21/3.42, flip angle 18 degrees, and field of view 200 mm]; and diffusion tensor images (voxel size $2 \times 2 \times 2.6$ mm and 64 noncollinear directions).

White matter hyperintensity volume was derived from T2-weighed FLAIR scans. In brief, a Gaussian curve was fit to map voxel intensity values. All voxels that were above 1.5 SDs from the image mean intensity were labeled. After manual edits of false positives, the remaining voxels were classified as WMHs. The number of labeled voxels was summed and multiplied by voxel dimensions to yield total WMHs volumes in cubic centimeters.[20] From T1 and FLAIR images, silent brain infarcts and dilated perivascular spaces were ascertained using a pathology-informed algorithm previously described with good to excellent reliability.[21] Diffusion tensor imaging images were eddy current corrected, and fractional anisotropy (FA) and mean diffusivity (MD) maps were computed using the functional magnetic resonance imaging of the brain Diffusion Toolbox (FMRIB software library v6.0 fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Each subject's FA and MD maps was normalized and projected onto a mean FA tract skeleton using the FMRIB software library tract-based spatial statistics . The mean FA and MD were computed from these skeletonized images using tracts of interest from the JHU-ICBM-DTI-81 white matter labels atlas. Abnormal white matter integrity was defined by the highest FA quartile and lowest MD quartile. The brain MRA was read by 2

readers using the warfarin-aspirin symptomatic intracranial disease criteria to define stenosis.[22] Intracranial large artery stenosis was defined as any luminal stenosis > 50% in the major branches of the circle of Willis and vertebrobasilar system. Examples of these MRI phenotypes are shown in Figure 1.

Statistical Analysis

Descriptive statistics were used to calculate the demographic characteristics and vascular risk factors of the study participants.

Neurocognitive Domains

Participants' scores on each of the neuropsychological measures were transformed into z scores to permit comparison across the different domains of cognitive and neuropsychiatric functioning using the mean and SD values of the study sample. SPSS package v20 (IBM SPSS Statistics, Armonk, NY) was used to conduct the factor analysis. Principal component analysis with oblimin rotation was used to explore the factors underlying the neurocognitive variables. All neurocognitive measures were considered for the initial analysis. The number of factors to be retained was guided by Kaiser criterion (eigenvalues > 1)[23] and visual inspection of the scree plot. We labeled each factor with guidance from a neuropsychologist to characterize the items loading on a domain. We considered loadings of >0.40 to reflect a variable selectively loading on a given factor to characterize the data. The reliability of the variables in each factor was assessed using Cronbach alpha coefficients > 0.80. The factor analysis yielded a 5-factor model that included working memory, paragraph memory/naming, list learning, mental sequencing, and speed. We obtained a global cognitive score by averaging the z scores of these 5 domains.

After the factor analysis, we conducted linear regression models for each cognitive domain separately with the following exposure variable for each model: silent brain infarcts, upper quartile of WMHs volume, abnormal white matter integrity, microhemorrhages, perivascular spaces, and intracranial large artery stenosis. We adjusted for demographic and vascular risk factors (which included hypertension, diabetes, dyslipidemia, and current smoking) in addition to status of HIV infection (controlled versus not controlled). Given small sample size, we considered a P value between 0.20 and 0.05 suggestive of a trend and a P value of <0.05 as statistically significant. We chose the exposure variable that emerged with at least a trend to form a cumulative CVD score to evaluate the impact of the cumulative CVD score in cognition.

RESULTS

The sample was composed of 85 participants (mean age 60 ± 6 years, 48% men, 78% non-Hispanic Black). Demographic characteristics are summarized in Table 1. Most of them had hypertension (66%) and well-controlled HIV (75%, defined by CD4 cell count > 200 cells/mm^3 and viral load < 400 copies/mL at or near the time of the MRI visit). One-third of the sample (33%) had evidence of silent

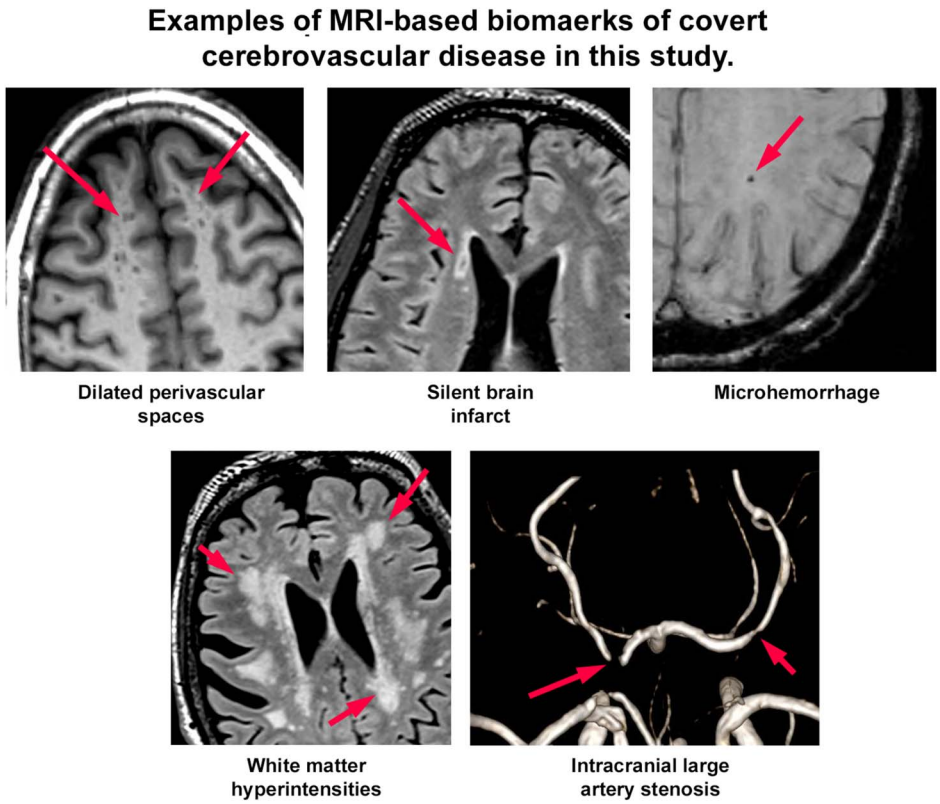

Figure 1. Examples of MRI-based biomaerks of covert CVD in this study. full color online

TABLE 1. Sample Characteristics (N = 85)

Age (in yrs, mean ± SD, range)	60 ± 6, 50–75
Men, %	48
Ethnicity	
Non-Hispanic Black	78%
Hispanic	22%
Education attainment	
Incomplete high school or lower	26%
Completed high school	23%
Some college	25%
College or higher	26%
Hypertension	66%
Diabetes	18%
Dyslipidemia	37%
Current smoking	48%
Viral load > 400 copies/mL	20%
CD4 cell count (mean ± SD)	636 ± 356
CD4 cell count < 200 cells/mm^3	10%
Nadir CD4 < 200 cells/mm^3	65%
Silent brain infarcts	33%
Microhemorrhages	5%
White matter hyperintensity volume (median, mean ± SD)	4.34, 6.2 ± 6.1
White matter abnormal microstructure	44%
Intracranial large artery stenosis	12%

brain infarcts, 5% of microhemorrhages, and 12% of intracranial large artery stenosis, and 44% had imaging evidence of abnormal white matter integrity as defined by a low FA and/or high MD.

In the univariate analysis, silent brain infarcts and intracranial large artery stenosis were associated with poorer cognition in at least one cognitive domain (Table 2). The association between silent brain infarcts and poorer cognition attenuated after adjustment for vascular risk factors and demographic covariates, whereas the association between intracranial large artery stenosis and list learning remained significant. Abnormal white matter integrity was associated with poorer mental sequencing and global cognition only after adjusting for demographics and education. There was no statistical association or trends between WMHs volume, microhemorrhages, or perivascular spaces with cognitive performance.

In a post hoc analysis, we created a score that reflected the cumulative burden of MRI-based biomarkers of covert CVD in PLWH (CVD score) by adding on the covert MRI-based biomarkers of CVD that scored at least a trend of an association with any of the 5 cognitive domains. We used silent brain infarcts, abnormal white matter integrity, and intracranial large artery stenosis to create the score (range 0–3) based on the results described in Table 2. The CVD score was 0 in 36% of participants, 1 in 46%, 2 in 13%, and 3 in 5%. In the adjusted models for age, sex, ethnicity, education attainment, vascular risk factors, ApoE4, and status of HIV infection, CVD score was associated with lower working memory (B = −0.213, P = 0.028), list learning (B = −0.275, P = 0.019), global cognition (B = −0.129, P = 0.007), and a trend toward lower mental sequencing (B = −0.099, P = 0.08). Other predictors of cognitive performance in these models are reported in Table 3.

DISCUSSION

We presented data from a cross-sectional study of 85 PLWH who underwent a brain MRI to assess for MRI-based biomarkers of covert CVD and related these to cognitive performance. We found that the presence of silent brain infarcts, abnormal white matter integrity, and intracranial large artery stenosis relate to some aspects of cognition and that the cumulative prevalence of these 3 MRI biomarkers relates to poorer working memory, list learning, and global cognition. These associations were independent of sex, age, ethnicity, education, viral suppression, vascular risk factors, and ApoE4. Expectedly, higher education attainment was associated with better overall cognition. Findings from this study identified the following: (1) vascular exposures that may be modifiable and may, therefore, influence cognition in PLWH; and (2) PLWH at higher risk of cognitive decline for testing targeted treatment.

Covert CVD represents an important contributor to cognition and dementia. This has been well established in non–HIV-infected cohorts, but this is the first study to provide evidence of this relationship in PLWH using a comprehensive array of covert MRI-based biomarkers of CVD, including brain arterial imaging, an often neglected marker of brain health. Compared with clinically overt CVD such as stroke, covert CVD is at least 3 to 4 times more frequent.[24] Furthermore, covert CVD is a risk factor of stroke and dementia.[14,25,26] Therefore, timely identification of covert CVD and understanding its role in stroke and dementia may help in identifying individuals at higher risk of future stroke and dementia, with the potential for intervention to prevent further decline.

Although there is extensive evidence relating these imaging biomarkers of covert CVD to cognition and dementia risk among people without HIV, there is less evidence of the role of these combined imaging biomarkers in PLWH. Most studies of covert CVD do not include a brain MRA or other types of arterial imaging to inform the status of brain large artery disease such as intracranial large artery stenosis. The study examining intracranial large artery stenosis in PLWH is of great importance because ethnic minorities are at an increased risk of both intracranial large artery stenosis and HIV.[27–29] Consequently, the inclusion of brain MRA in this work is a strength. The prevalence of intracranial stenosis has been studied mostly in the context of stroke and hospital-based samples[30–33] but not in nonstroke or the general HIV-infected populations. The prevalence of intracranial large artery stenosis was 12%, half of what has been reported in samples of hospitalized patients.[30] More importantly, intracranial large artery stenosis was a predictor of poorer verbal learning, independent of vascular risk factors, HIV control, and ApoE4. These findings mirror other non–HIV-infected cohorts.[12,34,35] Nonetheless, the pathophysiology of the association remains uncertain, and there is partial evidence that intracranial large artery stenosis may decrease brain blood flow,[36,37] which may trigger downstream mechanisms, leading to neurodegeneration in addition to increased risk of stroke. Other nonatherosclerotic arteriopathies such as dolichoectasia

TABLE 2. Association Between MRI-Based Biomarkers of Covert CVD and Cognitive Performance Among People Living With HIV

	Working Memory	Paragraph Memory/ Naming	List Learning	Mental Sequencing	Speed	Global Cognition
Silent brain infarcts						
Model 1	−0.34 ± 0.15*	−0.01 ± 0.19	−0.22 ± 0.19	−0.17 ± 0.09‡	−0.01 ± 0.11	−0.16 ± 0.08*
Model 2	−0.28 ± 0.16†	0.08 ± 0.19	−0.22 ± 0.19	−0.14 ± 0.09	−0.03 ± 0.12	−0.12 ± 0.08
Model 3	−0.29 ± 0.16†	0.06 ± 0.19	−0.23 ± 0.19	−0.17 ± 0.09†	−0.02 ± 0.12	−0.13 ± 0.08†
White matter hyperintensity volume upper quartile						
Model 1	0.08 ± 0.17	0.01 ± 0.19	0.16 ± 0.22	−0.09 ± 0.11	−0.11 ± 0.12	0.09 ± 0.09
Model 2	0.14 ± 0.18	0.01 ± 0.20	0.25 ± 0.21	−0.04 ± 0.11	−0.11 ± 0.13	0.04 ± 0.09
Model 3	0.15 ± 0.18	−0.01 ± 0.20	0.22 ± 0.21	−0.05 ± 0.11	−0.14 ± 0.13	−0.02 ± 0.09
Lowest FA quartile plus highest MD quartile						
Model 1	−0.03 ± 0.13	0.14 ± 0.16	−0.20 ± 0.16	−0.08 ± 0.08	−0.09 ± 0.10	−0.03 ± 0.07
Model 2	−0.08 ± 0.15	0.08 ± 0.18	−0.13 ± 0.17	−0.17 ± 0.09†	−0.08 ± 0.12	−0.09 ± 0.08
Model 3	−0.13 ± 0.15	0.10 ± 0.18	−0.10 ± 0.18	−0.17 ± 0.09†	−0.05 ± 0.12	−0.09 ± 0.07†
Microhemorrhages						
Model 1	−0.26 ± 0.35	0.59 ± 0.42	0.42 ± 0.42	−0.13 ± 0.20	−0.16 ± 0.24	0.10 ± 0.18
Model 2	−0.34 ± 0.35	0.50 ± 0.40	0.46 ± 0.41	−0.15 ± 0.21	−0.15 ± 0.25	0.07 ± 0.18
Model 3	−0.27 ± 0.35	0.58 ± 0.41	0.45 ± 0.43	−0.21 ± 0.21	−0.14 ± 0.26	0.08 ± 0.18
Perivascular spaces						
Model 1	0.03 ± 0.02	<0.001 ± 0.02	0.02 ± 0.02	0.01 ± 0.01	0.003 ± 0.01	0.01 ± 0.01
Model 2	0.02 ± 0.02	−0.01 ± 0.02	0.02 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Model 3	0.02 ± 0.02	−0.01 ± 0.02	0.02 ± 0.02	0.02 ± 0.01	0.005 ± 0.01	0.01 ± 0.01
Intracranial large artery stenosis						
Model 1	−0.06 ± 0.24	−0.25 ± 0.29	−0.74 ± 0.28*	0.12 ± 0.15	0.21 ± 0.17	−0.12 ± 0.12
Model 2	−0.05 ± 0.24	−0.26 ± 0.30	−0.72 ± 0.27*	0.08 ± 0.15	0.19 ± 0.17	−0.13 ± 0.12
Model 3	−0.02 ± 0.25	−0.39 ± 0.28	−0.69 ± 0.28*	0.21 ± 0.16	0.20 ± 0.18	−0.16 ± 0.12

Model 1, univariate analysis; model 2, adjusted for age, sex, education, and ethnicity; model 3, adjusted for age, sex, education, ethnicity, vascular risk factors (hypertension, diabetes, smoking, and dyslipidemia), *ApoE4* genotype, and well-controlled HIV (suppressed viral load and CD4 cell count > 200 cells/mm^3).All models for white matter disease were adjusted by total cranial volume.

*Identifies statistical significance with a P value < 0.05.

†Identifies an existing trend with a P value < 0.10.

(consisting of dilated brain arteries) are associated with poorer cognition, higher risk of dementia, and, among PLWH, longer and deeper immunosuppression.[11,31,38,39] Therefore, inclusion of brain MRA for systematic evaluation of such brain large artery phenotypes provides new insights into the role of brain large artery disease in HAND and other cerebral outcomes in PLWH.

WMHs volume and/or integrity are imaging biomarkers of covert CVD frequently studied among PLWH. For example, WMHs have been associated with decreased frontal cortical volume,[26] longer duration of HIV infection,[40] and aging.[41] Although we did not find any association between WMHs volume and cognition, markers of abnormal integrity in white matter such as low FA and high MD did show a trend toward poorer cognition, a finding replicated in some[42,43] but not all studies.[44] The etiology of white matter disease in people with HIV has been attributed to aging, hypertension, historical effects of AIDS (with gliosis, which seems white in FLAIR images), and ongoing neuroinflammation.[41,43,44] Intensive blood pressure control reduces the risk of mortality, vascular events (including stroke), and cognitive impairment in people without HIV.[45–49] Therefore, it is likely that the same benefit would likely be achieved for hypertensive PLWH, especially for PLWH who experience disproportionate burden of traditional risk factors (eg hypertension, diabetes, dyslipidemia, and smoking) and vascular disease.[2,50] It is less clear, however, whether modifying other therapeutic targets such as neuroinflammation could prevent, delay, or improve cognition in PLWH. This hypothesis may be worth exploring in future studies.

The prevalence of silent brain infarcts in this cohort is higher than what is reported elsewhere (33% versus 4%).[51] The disparity may be partly due to differences in definition of silent brain infarcts, variability in health care systems across countries (the United States versus France), and the underlying vascular health of the samples being compared. Prevalent silent brain infarcts in our study sample were associated with poorer language fluency and global cognition, and these associations attenuated after adjusting for vascular risk factors and demographics, suggesting that these confounders may partially mediate the effects of silent brain infarcts on cognition. The prevalence of silent brain infarcts has been extensively studied in people without HIV and consistently

TABLE 3. Role of Cerebrovascular Score in Cognition Among PLWH

	Working Memory	Paragraph Memory/Naming	List Learning	Mental Sequencing	Speed	Global Cognition
	B Estimate ± SE					
Age (in yr)	0.006 ± 0.013	0.027 ± 0.015	−0.030 ± 0.015†	0.009 ± 0.008	−0.005 ± 0.010	−0.003 ± 0.006
Men	0.019 ± 0.179	0.115 ± 0.213	−0.393 ± 0.214†	0.079 ± 0.106	−0.071 ± 0.137	−0.015 ± 0.088
Non-Hispanic Black	−0.115 ± 0.181	0.073 ± 0.215	0.073 ± 0.217	−0.166 ± 0.107	−0.062 ± 0.137	−0.050 ± 0.088
Education attainment (ordinally)	0.098 ± 0.048*	0.097 ± 0.059	0.131 ± 0.062*	0.068 ± 0.031*	−0.036 ± 0.037	0.069 ± 0.024*
ApoE4	0.294 ± 0.164†	0.028 ± 0.195	−0.142 ± 0.196	0.006 ± 0.097	−0.025 ± 0.125	0.044 ± 0.081
Sum of vascular risk factors (range 0–4)	−0.066 ± 0.091	0.129 ± 0.093	−0.167 ± 0.094†	0.018 ± 0.047	0.024 ± 0.059	−0.004 ± 0.038
Well-controlled HIV	−0.092 ± 0.172	0.030 ± 0.204	−0.024 ± 0.207	−0.117 ± 0.102	0.122 ± 0.132	−0.016 ± 0.084
Cumulative cerebrovascular score (range 0–3)	−0.213 ± 0.095*	−0.053 ± 0.113	−0.275 ± 0.114*	−0.099 ± 0.056†	0.046 ± 0.076	−0.129 ± 0.046*

*identifies statistical significance with $P < 0.05$.
†identifies a trend defined by a P value 0.05–0.10.

reported to be associated with higher risk of vascular events,[25] dementia,[15] and poorer cognition.[52] Given the disparities in traditional risk factor among PLWH, it is not surprising that silent brain infarcts are more common among PLWH than in HIV-negative controls. Although there are no findings from randomized trials to firmly support a specific clinical algorithm among people with incidentally found silent brain infarcts, independent of HIV status, the difference between silent brain infarcts and stroke is explained better by silent brain infarcts localization in more a clinically silent area (left hemisphere) and smaller infarct size than a different pathophysiology of silent brain infarcts compared with strokes.[24] Further research on this topic would help in guiding clinical management of people with incidentally found silent brain infarcts, but the data from this study support the notion that silent brain infarcts are important determinants of poorer cognition in PLWH.

In post hoc analyses, we found that a composite score representing the cumulative prevalence of silent brain infarcts, white matter abnormal integrity, and intracranial large artery stenosis was associated with poorer cognition in PLWH. Cumulative brain injury may decrease brain plasticity and remodeling to allow for compensation in the expected cognitive deficit. The cumulative prevalence of these imaging biomarkers may also reflect more severe vascular disease, which in turn could represent an epiphenomenon of poorer vascular health. Because of the heterogeneous prevalence of the individual component of the vascular score, we cannot infer the relative weight of each of them in the individual component of cognition. In a relatively small sample such as ours, the additive model of effect size attributed to each biomarker may improve power to detect an association with cognition. The sample size made it difficult to evaluate the individual association between individual vascular risk factors and the imaging biomarkers. Similarly, results in Table 2 would not survive multiple comparison adjustment and should be considered preliminary. Nonetheless, intense therapy of the 4 main modifiable vascular risks (eg, hypertension, diabetes, dyslipidemia, and smoking) is a goal that should be pursued regardless of whether or not these risk factors were related to poorer cognition. Replication of these results in samples that include other racial and ethnic groups and less urban setting may increase the certainty of the association between covert MRI-based biomarkers of CVD and poorer cognition to a broader HIV population. Finally, the relationship between CVD and Alzheimer pathology in the aging HIV population remains a relative underexplored area that may yield new insights into HAND.

ACKNOWLEDGMENTS

The authors thank the participants for their time and effort volunteering for this study.

REFERENCES

1. McArthur JC, Hoover DR, Bacellar H, et al. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. *Neurology.* 1993;43:2245–2252.
2. Gutierrez J, Albuquerque ALA, Falzon L. HIV infection as vascular risk: a systematic review of the literature and meta-analysis. *PLoS One.* 2017; 12:e0176686.
3. Gallant JE, Moore RD, Richman DD, et al. Incidence and natural history of cytomegalovirus disease in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology Study Group. *J Infect Dis.* 1992;166:1223–1227.
4. Brightbill TC, Ihmeidan IH, Post MJ, et al. Neurosyphilis in HIV-positive and HIV-negative patients: neuroimaging findings. *AJNR Am J Neuroradiol.* 1995;16:703–711.
5. Whiteman M, Espinoza L, Post MJ, et al. Central nervous system tuberculosis in HIV-infected patients: clinical and radiographic findings. *AJNR Am J Neuroradiol.* 1995;16:1319–1327.
6. Gillams AR, Allen E, Hrieb K, et al. Cerebral infarction in patients with AIDS. *AJNR Am J Neuroradiol.* 1997;18:1581–1585.
7. Williams DW, Eugenin EA, Calderon TM, et al. Monocyte maturation, HIV susceptibility, and transmigration across the blood brain barrier are critical in HIV neuropathogenesis. *J Leukoc Biol.* 2012;91:401–415.
8. Valcour V, Chalermchai T, Sailasuta N, et al. Central nervous system viral invasion and inflammation during acute HIV infection. *J Infect Dis.* 2012;206:275–282.
9. Kamat A, Lyons JL, Misra V, et al. Monocyte activation markers in cerebrospinal fluid associated with impaired neurocognitive testing in advanced HIV infection. *J Acquir Immune Defic Syndr.* 2012;60: 234–243.

10. Yuan L, Qiao L, Wei F, et al. Cytokines in CSF correlate with HIV-associated neurocognitive disorders in the post-HAART era in China. *J Neurovirol.* 2013;19:144–149.
11. Gutierrez J, Guzman V, Khasiyev F, et al. Brain arterial dilatation and the risk of Alzheimer's disease. *Alzheimers Dement.* 2019;15:666–674.
12. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. *Neurology*. 2005;64:494–500.
13. Kalback W, Esh C, Castaño EM, et al. Atherosclerosis, vascular amyloidosis and brain hypoperfusion in the pathogenesis of sporadic Alzheimer's disease. *Neurol Res.* 2004;26:525–539.
14. Brickman AM, Provenzano FA, Muraskin J, et al. Regional white matter hyperintensity volume, not hippocampal atrophy, predicts incident Alzheimer disease in the community. *Arch Neurol.* 2012;69:1621–1627.
15. Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med.* 2003;348: 1215–1222.
16. Tatemichi TK, Paik M, Bagiella E, et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. *Neurology.* 1994; 44:1885–1891.
17. Chi NF, Chien LN, Ku HL, et al. Alzheimer disease and risk of stroke: a population-based cohort study. *Neurology.* 2013;80:705–711.
18. Robinson-Papp J, Navis A, Dhamoon MS, et al. The use of visual rating scales to quantify brain MRI lesions in patients with HIV infection. *J Neuroimaging.* 2018;28:217–224.
19. Peluso MJ, Meyerhoff DJ, Price RW, et al. Cerebrospinal fluid and neuroimaging biomarker abnormalities suggest early neurological injury in a subset of individuals during primary HIV infection. *J Infect Dis.* 2013;207:1703–1712.
20. Brickman AM, Tosto G, Gutierrez J, et al. An MRI measure of degenerative and cerebrovascular pathology in Alzheimer disease. *Neurology.* 2018;91:e1402–e1412.
21. Gutierrez J, Elkind MS, Cheung K, et al. Pulsatile and steady components of blood pressure and subclinical cerebrovascular disease: the Northern Manhattan Study. *J Hypertens.* 2015;33:2115–2122.
22. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* 2005;352:1305–1316.
23. Kaiser HF. The application of electronic computers to factor analysis. *Educ Psychol Meas.* 1960;20:141–151.
24. Gutierrez J, Gil-Guevara A, Ramaswamy S, et al. Classification of covert brain infarct subtype and risk of death and vascular events. *Stroke.* 2020; 51:90–98.
25. Wright CB, Dong C, Perez EJ, et al. Subclinical cerebrovascular disease increases the risk of incident stroke and mortality: the Northern Manhattan study. *J Am Heart Assoc.* 2017;6:e004069.
26. McMurtray A, Nakamoto B, Shikuma C, et al. Cortical atrophy and white matter hyperintensities in HIV: the Hawaii Aging with HIV Cohort Study. *J Stroke Cerebrovasc Dis.* 2008;17:212–217.
27. Qiao Y, Guallar E, Suri FK, et al. MR imaging measures of intracranial atherosclerosis in a population-based study. *Radiology.* 2016;280:860–868.
28. Suri MFK, Qiao Y, Ma X, et al. Prevalence of intracranial atherosclerotic stenosis using high-resolution magnetic resonance angiography in the general population. The Atherosclerosis Risk in Communities Study. *Stroke.* 2016;47:1187–1193.
29. Silverberg MJ, Leyden W, Quesenberry CP Jr, et al. Race/ethnicity and risk of AIDS and death among HIV-infected patients with access to care. *J Gen Intern Med.* 2009;24:1065–1072.
30. Edwards NJ, Grill MF, Choi HA, et al. Frequency and risk factors for cerebral arterial disease in a HIV/AIDS neuroimaging cohort. *Cerebrovasc Dis.* 2016;41:170–176.
31. Gutierrez J, Goldman J, Dwork AJ, et al. Brain arterial remodeling contribution to nonembolic brain infarcts in patients with HIV. *Neurology.* 2015;85:1139–1145.
32. Gutierrez J, Hatleberg CI, Evans H, et al. Role of pre-stroke immunity in ischemic stroke mechanism among patients with HIV. *AIDS Care.* 2018: 1–5.
33. Vinikoor MJ, Napravnik S, Floris-Moore M, et al. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the Southeastern United States. *AIDS Res Hum Retroviruses.* 2013;29: 1068–1074.
34. Dolan H, Crain B, Troncoso J, et al. Atherosclerosis, dementia, and Alzheimer disease in the Baltimore longitudinal study of aging cohort. *Ann Neurol.* 2010;68:231–240.
35. Roher AE, Esh C, Rahman A, et al. Atherosclerosis of cerebral arteries in Alzheimer disease. *Stroke*. 2004;35(11 suppl 1):2623–2627.
36. Nixon AM, Gunel M, Sumpio BE. The critical role of hemodynamics in the development of cerebral vascular disease. *J Neurosurg.* 2010;112: 1240–1253.
37. Kamouchi M, Kishikawa K, Okada Y, et al. Poststenotic flow and intracranial hemodynamics in patients with carotid stenosis: transoral carotid ultrasonography study. *AJNR Am J Neuroradiol.* 2005;26:76–81.
38. Gutierrez J, Menshawy K, Gonzalez M, et al. Brain large artery inflammation associated with HIV and large artery remodeling. *AIDS.* 2016;30:415–423.
39. De Alwis PM, Smith BR, Wu T, et al. In-vivo MRI reveals changes to intracerebral vasculature caliber in HIV infection. *Front Neurol.* 2019; 10:687.
40. Trentalange A, Prochet A, Imperiale D, et al. Cerebral white matter Hyperintensities in HIV-positive patients. *Brain Imaging Behav.* 2020; 14:10–18.
41. Seider TR, Gongvatana A, Woods AJ, et al. Age exacerbates HIV-associated white matter abnormalities. *J Neurovirol.* 2016;22:201–212.
42. Ragin AB, Storey P, Cohen BA, et al. Whole brain diffusion tensor imaging in HIV-associated cognitive impairment. *AJNR Am J Neuroradiol.* 2004;25:195–200.
43. van Zoest RA, Underwood J, De Francesco D, et al. Structural brain abnormalities in successfully treated HIV infection: associations with disease and cerebrospinal fluid biomarkers. *J Infect Dis.* 2017;217:69–81.
44. Su T, Caan MW, Wit FW, et al. White matter structure alterations in HIV-1-infected men with sustained suppression of viraemia on treatment. *AIDS.* 2016;30:311–322.
45. Lithell H, Hansson L, Skoog I, et al. The study on cognition and prognosis in the elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens.* 2003;21:875–886.
46. Forette F, Seux ML, Staessen JA, et al. Prevention of dementia in randomised double-blind placebo-controlled systolic hypertension in Europe (Syst-Eur) trial. *Lancet.* 1998;352:1347–1351.
47. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA.* 1996; 276:1886–1892.
48. Group TSMIftSR. Effect of intensive vs standard blood pressure control on probable dementia: a randomized clinical trial. *JAMA.* 2019;321: 553–561.
49. SPRINT A. Randomized trial of intensive versus standard blood-pressure control. *New Engl J Med.* 2015;373:2103–2116.
50. Gutierrez J, Elkind MSV, Marshall RS. Cardiovascular profile and events of US adults 20–49 years with HIV: results from the NHANES 1999–2008. *AIDS Care.* 2013:1–7.
51. Moulignier A, Savatovsky J, Assoumou L, et al. Silent cerebral small-vessel disease is twice as prevalent in middle-aged individuals with well-controlled, combination antiretroviral therapy–treated human immunodeficiency virus (HIV) than in HIV-uninfected individuals. *Clin Infect Dis.* 2017;66:1762–1769.
52. Huijts M, Duits A, van Oostenbrugge RJ, et al. Accumulation of MRI markers of cerebral small vessel disease is associated with decreased cognitive function. A study in first-ever Lacunar stroke and hypertensive patients. *Front Aging Neurosci.* 2013;5:72.