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Plasma biomarkers of vascular dysfunction uniquely relate to a vascular-risk profile of neurocognitive deficits in virally-suppressed adults with HIV

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ABSTRACT

Objective: Chronic inflammation and vascular dysfunction (e.g., chronic endothelial activation) are related yet dissociable mechanisms of HIV-associated neurocognitive impairment (NCI), even among those on antiretroviral therapy (ART). However, how these mechanisms differentially contribute to domain-specific deficits in people with and without HIV (PWH, PWoH) is unclear. We empirically-derived profiles of NCI and examined relationships with peripheral inflammatory and vascular biomarkers.

Methods: Participants were 84 virally-suppressed PWH and 126 PWoH who underwent neuropsychological testing and blood draw. Cluster analysis identified subgroups based on domain deficit scores. ANOVAs examined HIV serostatus and cluster group differences in composite plasma biomarker z-scores of inflammation (IL-6, CXCL10/IP-10, CCL2/MCP-1) and vascular injury (VCAM-1, ICAM-1, uPAR). Confirmatory regressions examined the interaction of HIV and biomarker z-scores on domain-specific T-scores, controlling for cardiovascular disease (CVD) risk and psychosocial factors.

Results: Cluster analysis identified three groups: *Unimpaired* (n = 129), *Learning/Recall* (n = 52, isolated learning/recall deficits), *Dysexecutive/Slow* (n = 29, executive function, working memory, processing speed, and motor deficits). PWH had higher odds of *Dysexecutive/Slow* membership, which related to CVD risk and higher vascular dysfunction, but not inflammation, in PWH. Vascular biomarkers moderated adverse HIV effects on executive function, processing speed, and working memory such that PWH had lower T-scores only when vascular dysfunction was high.

Conclusions: In PWH with controlled disease, peripheral markers of endothelial dysfunction and vascular permeability are selectively associated with an empirically-derived subgroup that exhibits domain deficits commonly impacted by cerebrovascular disease. Findings support the presence of a vascular NCI subgroup of PWH who may benefit from interventions that directly target the neurovascular unit.

1. Introduction

Antiretroviral therapy (ART) has dramatically improved the survival and quality of life of people with HIV (PWH). However, HIV-associated neurocognitive disorders (HAND) remain highly prevalent, particularly in milder forms (Sacktor and Robertson, 2014) and even in PWH on suppressive ART (Heaton et al., 2010). The most prominent neurocognitive deficits in the ART era tend to be observed in the domains of learning and executive function, though many PWH are also impaired in delayed recall, processing speed, working memory, and motor skills (Heaton et al., 2011; Sacktor, 2018). Significant heterogeneity exists with regard to severity and profile of neurocognitive impairment (NCI) in PWH (Sacktor, 2018) and this is also reflected in neuroimaging (Jernigan et al., 2011) and neuropathological (Everall et al., 2009) studies. One explanation for this heterogeneity is that there may be subtypes of HAND with distinct underlying mechanisms, risk factors,

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and consequences. Identifying subtypes of HAND may improve our understanding of the etiology, nature, course, and treatment of HAND.

Multiple factors contribute to NCI in virally suppressed PWH (Winston and Spudich, 2020), including viral persistence in the CNS (Anderson et al., 2016), cellular and epigenetic factors (Corley et al., 2016; Kallianpur and Levine, 2014), ART toxicity (Ciccarelli et al., 2011; Hakkers et al., 2019), comorbidities (e.g., hypertension, metabolic syndrome (Guzman et al., 2021; Yu et al., 2019);), and coinfections (e.g., cytomegalovirus (Letendre et al., 2018);). A unifying factor across these mechanisms is chronic immune activation and inflammation. ART reduces, but does not normalize immune activation, in most PWH. Soluble biomarkers of immune activation and inflammation are elevated in PWH despite viral suppression (Edén et al., 2007; Hattab et al., 2015; Neuhaus et al., 2010) and in PWH with HAND (Bandera et al., 2019; Montoya et al., 2019). This persistent level of low-grade chronic immune activation and inflammation, which induces neuroinflammation and neurovascular complications (Everall et al., 2009; Gelman, 2015; Hsue et al., 2004), is considered a key element of pathogenesis of NCI in ART-treated PWH.

Chronic inflammation in ART-treated PWH can also lead to endothelial dysfunction (Melendez et al., 2008; Ross et al., 2009), which is a key mechanism underlying the development of atherosclerosis and subsequent cardiovascular disease (CVD). During the immune response to infection, pro-inflammatory cytokines released from immune cells activate endothelial cells, triggering the expression of cellular adhesion molecules (e.g., ICAM-1, VCAM-1). Cell adhesion molecules interact with other molecules (e.g., chemokine CCL2/MCP-1) to promote the recruitment, adherence, and migration of leukocytes to and across the vascular endothelium (Chistiakov et al., 2015; Lo and Plutzky, 2012). Chronic and sustained activation of immune and endothelial cells leads to increased adhesion molecule expression, vascular permeability, and immune cell migration, which further propogates the inflammatory response and can lead to endothelial dysfunction (loss or alteration of physiological functions of the endothelium [e.g., regulating vascular tone, permeability, and inflammation]) or damage (i.e., attacks on endothelial integrity).

CVD is among the most prevalent of age-associated non-infectious conditions in PWH (Caetano et al., 2022; Shah et al., 2018), may occur at earlier ages relative to age-matched people without HIV (Antiretroviral Therapy Cohort, 2010; Krikke et al., 2017), and is further exacerbated by the increased incidence of traditional (e.g., diabetes, smoking) and non-traditional risk factors (e.g., substance use, hepatitis C) (Demir et al., 2018). In the general population, CVD, particularly in mid-life, is among the strongest risk factors for vascular, Alzheimer's, and mixed dementia types (Panza et al., 2012). Studies of PWH, including those who are virally suppressed, have found adverse independent effects of CVD and/or its risk factors on NCI (Chow et al., 2020; Guzman et al., 2021; McIntosh et al., 2021; Pasipanodya et al., 2019), brain inflammation, vascular abnormalities, and neural injury (Cysique et al., 2013; Moulignier and Costagliola, 2020). As the HIV population grows older, CVD and its risk factors are increasingly recognized for their role in HAND.

Recent studies have also found evidence of endothelial dysfunction and blood-brain barrier (BBB) impairment in ART-treated and virally-suppressed PWH (Caligaris et al., 2021; Ellis et al., 2021; Gelman, 2015; Kristoffersen et al., 2009; Melendez et al., 2008; Ross et al., 2009). The BBB, composed of specialized endothelial cells and tight junctions and surrounded by a basement membrane, pericytes, astrocytes, microglia and neurons (Atluri et al., 2015; De Benedetto et al., 2020; Marincowitz et al., 2019), is a primary target of HIV-associated neural injury (Eugenin et al., 2006; Williams et al., 2012) and a central neuropathological factor underlying HAND (Cysique and Brew, 2019; Gelman, 2015; Gelman et al., 2012). The BBB is also altered by CVD, further contributing to dysfunction (Helman and Murphy, 2016). Increased BBB permeability is a key mechanism in cognitive impairment due to cerebrovascular disease, which is similar to HAND in terms of risk factors and often has similar underlying pathological processes given evidence of overlapping neuroimaging and neurocognitive phenotypes (Cysique and Brew, 2019). Cerebrovascular-related cognitive deficits depend on the location and characteristics of the particular lesion(s), though these lesions are often distributed throughout fronto-subcortical and fronto-parietal white matter tracts important for processing speed and executive functioning (Vasquez and Zakzanis, 2015). These domains are also linked to subclinical CVD and atherosclerosis in PWH (Becker et al., 2009; Crystal et al., 2011; Huck et al., 2018; Montoya et al., 2017), and similar patterns of diffuse white matter pathology are found in HAND (Biesbroek et al., 2017; Cysique et al., 2017; Peng et al., 2018; Smail and Brew, 2018; Van Der Flier et al., 2018). Given these similarities and the aging HIV population, there is a heightened need to distinguish vascular from non-vascular presentations of HAND, though the standard method of classifying HAND using Frascati criteria (Antinori et al., 2007) would not be able to distinguish the two phenotypically (Brew et al., 2009).

Together these findings have generated increased interest in vascular contributions to NCI in ART-treated PWH (Cysique and Brew, 2019). Although chronic systemic inflammation and CVD have been linked to HAND, far less is known regarding the relationship between HAND and vascular mechanisms such as endothelial dysfunction that underlie the relationship between HIV, inflammation and vascular disease. Endothelial dysfunction can be assessed by measuring circulating levels of endothelial activation biomarkers (e.g., vascular cell adhesion molecule 1 [VCAM-1] and intercellular adhesion molecule 1 [ICAM-1]). Plasma levels ICAM-1 and VCAM-1 are elevated in treated PWH relative to people without HIV (PWoH (Mezoh and Crowther, 2019);) and associated with inflammation (Melendez et al., 2008), though their links to NCI in ART-treated PWH are unclear. Thus, the present study sought to examine the relative contributions of biomarkers reflective of endothelial cell activation and dysfunction (i.e., "vascular" biomarkers) and biomarkers of inflammation to empirically-derived, domain-based neurocognitive deficit profiles in a cohort of virally-suppressed PWH and HIV-seronegative adults. We hypothesized that vascular and inflammatory biomarker levels would differ across NCI profiles in the entire sample, but expected these biomarkers to be independently and most strongly associated with NCI profile(s) among PWH. Identification and validation of NCI profiles and their underlying biological substrates may help identify subtypes of HAND that will improve our understanding of its etiology in the ART era and inform diagnostic criteria that better detect earlier signs of HAND.

2. Methods

2.1. Participants

Participants were 84 HIV-seropositive (HIV+) and 126 HIV-seronegative (HIV-) adults enrolled in the University of California San Diego's (UCSD) Translational Methamphetamine AIDS Research Center (TMARC). Study visits took place between 2009 and 2020 and all participants provided written informed consent to study procedures, which were approved by the UCSD Institutional Review Board. Exclusion criteria for the parent study, TMARC, were history of psychotic disorder, HCV co-infection, or presence of a neurological condition (e.g., stroke, epilepsy, history of moderate or severe traumatic brain injury) that would confound the interpretation of neuropsychological test results and their association with HIV disease. In order to focus the current analyses exclusively on HIV, the present study also excluded TMARC participants who: 1) met criteria for a current substance use disorder (including methamphetamine); 2) reported illicit substance use in the past 90 days (except for cannabis), and/or; 3) had a positive urine toxicology screen for drugs (except cannabis) or positive breathalyzer test for alcohol on the day of testing. HIV + participants were also excluded from analysis if they had HIV RNA load >200 copies/ml. HIV serostatus was determined via self-report and confirmed with a finger

stick point-of-care test (MedMira Inc., Nova Scotia, Canada).

2.1.1. Neurocognitive assessment

Participants completed a comprehensive and validated neuropsychological assessment that encompassed an estimate of premorbid verbal IQ (i.e., Wide Range Achievement Test Reading subtest, Version 4 [WRAT4] (Wilkinson and Robertson, 2006) and seven neurocognitive domains commonly impacted by HIV (Heaton et al., 2010; Morgan et al., 2012; Rippeth et al., 2004). The domains and individual tests were: *verbal fluency* (Controlled Oral Word Association Test, animal fluency, action fluency), *executive function* (Wisconsin Card Sorting Test-64 Card Version, Trail Making Test B, Stroop Color and Word Test Interference Score), *processing speed* (Trail Making Test A, WAIS-III Digit Symbol, WAIS-III Symbol Search, Stroop Color and Word Test Color Score), *learning* and *delayed recall* (Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised), *working memory* (WMS-III Spatial Span, Paced Auditory Serial Addition Test), and *motor skills* (Grooved Pegboard Test).

For participants with previous test battery exposure due to prior research visits, raw scores for each test were converted to practice effect-adjusted scaled scores (Cysique et al., 2011). Scaled scores were converted to demographically-corrected T-scores that adjusted for the effects of age, education, sex, and race/ethnicity, as appropriate (Heaton et al., 2003, 2004; Norman et al., 2011). T-scores were averaged across the battery and within each domain to derive global and domain-specific T-scores. T-scores were also converted to deficit scores that give differential weight to impaired, as opposed to normal scores, on a scale ranging from 0 ($T \geq 40$; normal) to 5 ($T < 20$; severe impairment) (Blackstone et al., 2012; Carey et al., 2004). Deficit scores were used for cluster analysis (see *Statistical Analysis*) in order to identify neurocognitive subgroups characterized by impairment severity, and dichotomous impairment classifications (deficit score >0.5) were calculated to aid cluster group interpretation. T-scores were selected over deficit scores for multiple linear regression analyses (see *Statistical Analysis*), because their normal distribution better conforms to the parametric assumptions of linear regression.

2.1.2. Biomarker assays

Plasma for biomarker assays was collected using EDTA vacuum tubes via standard phlebotomy procedures. Soluble levels of inflammatory biomarkers (i.e., cytokine IL-6 and chemokines CXCL10/IP-10 and CCL2/MCP-1), and biomarkers reflective of endothelial activation and/or vascular permeability (cellular adhesion molecules ICAM-1 and VCAM-1, and uPAR) were measured using electrochemical luminescence immunoassays (MesoScale Discovery, Maryland). All assays were performed in duplicate. Assays were repeated when the coefficient of variation was greater than 20%. In addition, 10% of all assays were repeated to assess operator and batch consistency. To reduce the influence of batch variation, raw biomarker data was normalized on a plate-by-plate basis using median value across wells. Biomarkers were adjusted for batch variation and converted to z-scores to reduce skewness and facilitate interpretation. Individual biomarker z-scores were grouped and averaged to form separate composites z-scores for primary vascular (ICAM-1, VCAM-1, uPAR) and inflammatory processes (IL-6, CXCL10/IP-10, CCL2/MCP-1).

2.2. Medical and neuropsychiatric assessment

Participants also completed structured clinical interviews to determine medical and neuropsychiatric comorbidities. Medical comorbidities were determined based on the combination of self-report and/or specific drug treatment for the condition. Characterization of cardiometabolic risk included evaluation of hypertension, hyperlipidemia, diabetes mellitus, body mass index (BMI), and smoking history (both current and ever). Data for central adiposity, indexed via midwaist circumference (cm), was also available on a subset of participants (n = 141; 77 HIV-, 64 HIV+) and is presented for descriptive purposes. The Composite International Diagnostic Interview (CIDI (World Health Organization, 1998); was administered to determine DSM-IV diagnoses of current and lifetime Major Depressive Disorder (MDD) and substance use disorders (abuse or dependence). The Beck Depression Inventory-II (BDI-II) assessed for frequency and severity of depressive symptoms in the past two weeks (Beck et al., 1996).

2.3. Statistical Analysis

JMP Pro 16.0.0 was used for statistical analyses (SAS Institute Inc., Cary, NC, 2021). HIV serostatus differences on demographic, cardiometabolic, neuropsychiatric, biomarker, and neurocognitive variables were examined using analysis of variance (ANOVA), Wilcoxon/Kruskal-Wallis tests, and Chi-square statistics as appropriate. The relationship of vascular and inflammation composite z-scores with neurocognitive profiles was examined via a two-step approach that employed a person-centered, data-reduction method followed by a confirmatory multiple regression analysis. First, a data-driven cluster analysis of domain-specific deficit scores was performed to empirically-derive homogenous subpopulations of neurocognitive deficit profiles. We applied the JMP hierarchical agglomerative clustering function and the Ward method based on sum of squares to determine the distance between the clusters. The number of clusters is selected visually based on graphical representations (e.g., dendograms, constellation plots) and by examining the distance between clusters. Since this approach is primarily descriptive and determination of the optimal number of clusters also considers sample size, parsimony, and meaningful interpretation, we also conducted discriminant function analyses to evaluate the ability of domain deficit scores to discriminate the clusters derived from the hierarchical clustering analyses. These methods are consistent with those utilized in prior studies (Bondi et al., 2014).

To maximize sample size, the cluster analysis was conducted on 247 participants, which included the 210 individuals in the present study and 37 additional TMARC participants without biomarker data. These additional 37 participants (17 HIV-, 20 HIV+) had comparable demographic and clinical backgrounds to the 210 participants with biomarker data. Cluster group differences in vascular and inflammation z-scores were then examined in the full study sample (N = 210) and stratified by HIV serostatus. Cohen's *d* statistics are presented as estimates of effect size for pairwise comparisons.

Next, after interpreting the cluster analysis, we selected a subset of neurocognitive domains for multiple regression analysis based on the domains most impacted in the cluster group with the highest elevations in biomarker composite z-scores. In addition to limiting the number of domains, we controlled for multiple comparisons by only conducting multiple regressions for biomarker-domain relationships that exhibited significant univariable associations with the False Discovery Rate (FDR) set at 5% (Benjamini and Hochberg, 1995). The multiple regression analyses tested the interaction of HIV serostatus and biomarker composite z-scores on domain T-scores, adjusting for clinical factors that significantly differed (i.e., $p < .05$) by HIV serostatus or neurocognitive subgroups identified in the cluster analysis. The following variables were identified as having met our criterion for covariates: hypertension, hyperlipidemia, smoking status (ever), lifetime MDD, and BDI-II. Demographic variables (i.e., age, sex, education, race/ethnicity) were not included as covariates in neurocognitive analyses given that neurocognitive T-scores already adjusted for these factors. However, regression analyses also controlled for premorbid verbal intelligence (i.e., reading subscale of the WRAT-4) in order to account for differences in educational quality that may not be captured by test score adjustments for years of formal education (Manly et al., 2002).

3. Results

3.1. Participant characteristics

The full study sample was 56% non-Hispanic White and 70% male with a mean age of 43.5 years (range: 18–87) and mean education of 14.2 years. Participant characteristics by HIV serostatus are presented in Table 1. Groups were comparable with respect to age, education, estimated premorbid verbal IQ (WRAT-4), and race/ethnicity. The HIV + group expectedly had significantly more males than the HIV- group (89% vs. 57%). HIV + participants exhibited greater cardiometabolic risk, as indicated by higher rates of hyperlipidemia (29% vs. 12%) and lifetime smoking (82% vs. 64%). HIV + participants also reported more extensive depressive symptomatology, as indicated by higher median BDI-II scores (9 vs. 2) and higher rates of lifetime MDD (42% vs. 27%). HIV + individuals exhibited evidence of ART-induced immune recovery, as indicated by higher current CD4 counts (median = 652 cells/mm^3) compared to nadir CD4 counts (median = 245 cells/mm^3) and active ART use (98%). All HIV + participants were virally suppressed (i.e., plasma HIV viral load <200 copies/uL).

Table 1
Study sample characteristics (N = 210).

	PWoH (n = 126)	PWH (n = 84)	*p*
Demographics			
Age (years), mean (SD)	42.6 (15.6)	44.9 (13.0)	.268
Sex (male), n (%)	73 (57.0)	75 (89.3)	<.001
Education (years), mean (SD)	14.0 (2.3)	14.5 (2.3)	.124
WRAT4, mean (SD)	103.6 (14.0)	104.7 (11.8)	.547
Race/ethnicity			.946
Non-Hispanic White, n (%)	71 (56.3)	47 (56.0)	
Black, n (%)	17 (13.5)	12 (14.3)	
Hispanic, n (%)	29 (23.0)	19 (22.6)	
Asian, n (%)	5 (4.0)	2 (2.4)	
Other, n (%)	4 (3.2)	4 (4.8)	
Cardiometabolic Risk			
Body mass index, mean (SD)	28.20 (6.70)	27.66 (4.47)	.544
Midwaist Circumference (cm), mean (SD)[a]	94.5 (17.5)	98.5 (13.9)	.145
Diabetes, n (%)	8 (6.2)	3 (3.6)	.587
Hypertension, n (%)	21 (16.4)	21 (25.0)	.174
Hyperlipidemia, n (%)	15 (11.7)	24 (28.6)	.004
Ever smoker, n (%)[b]	80 (63.5)	69 (82.1)	.003
Current smoker, n (%)[c]	43 (34.7)	26 (32.5)	.865
Neuropsychiatric characteristics			
Lifetime Major Depressive Disorder, n (%)	34 (27.0)	35 (41.7)	.035
Current Major Depressive Disorder, n (%)[d]	4 (3.2)	8 (9.6)	.067
Beck Depression Inventory-II, median [IQR]	2 [0, 6]	9 [2, 16]	.003
Lifetime alcohol use disorder, n (%)	46 (36.5)	33 (39.3)	.653
Lifetime cannabis use disorder, n (%)	28 (22.2)	23 (27.4)	.378
Lifetime methamphetamine use disorder, n (%)	30 (23.4)	27 (32.1)	.215
HIV Disease Characteristics			
AIDS diagnosis, n (%)		36 (42.8)	
Estimated years of infection, median [IQR]		10 [3, 17]	
Nadir CD4 count, median [IQR]		245 [105, 411]	
Current CD4 count, median [IQR]		652 [497, 841]	
On ART, n (%)		82 (97.6)	
On protease inhibitor, n (%)		16 (19.3)	
Months on current regimen, median [IQR]		11.6 [4.9, 27.6]	
Months of lifetime ART exposure, median [IQR]		59.6 [22.5, 136.2]	

Note. ART = antiretroviral therapy; WRAT4 = Wide-Range Achievement Test, Reading subtest.
[a] N = 141.
[b] N = 208.
[c] N = 203.
[d] Current indicates meeting diagnostic criteria within the last 30 days.

3.2. HIV serostatus differences in neurocognition and plasma biomarkers

HIV serostatus differences in neurocognitive T-scores and deficit scores are presented in Table 2. HIV + status was related to significantly poorer global neurocognition, both in terms of lower global T-scores ($d = -0.38$, $p = .007$) and higher global deficit scores ($d = 0.29$, $p = .042$). HIV + individuals exhibited poorer scores across most domains, however the global effect was primarily driven by statistically significant, small-to-medium sized differences in executive function, processing speed, and working memory.

Vascular and inflammation z-scores exhibited a positive, medium-sized correlation in the full study sample ($r = 0.53$, $p < .001$) and within serostatus groups (HIV-: $r = 0.53$, $p < .001$; HIV+: $r = 0.48$, $p < .001$). Compared to HIV-, HIV + individuals exhibited significantly higher vascular ($d = 0.32$, $p = .025$) and inflammation z-scores ($d = 0.68$, $p < .001$; Table 3). With respect to individual components of the vascular composite, VCAM-1 z-scores were significantly higher in HIV + individuals ($d = 0.52$, $p < .001$), whereas ICAM-1 and uPAR z-scores did not differ by HIV serostatus ($ps > .144$). With respect to individual components of the inflammation composite, CXCL10/IP-10 ($d = 0.78$, $p < .001$) and CCL2/MCP-1 ($d = 0.49$, $p < .001$) were significantly higher in HIV + individuals, whereas differences in IL-6 z-scores ($d = 0.24$, $p = .093$) approached statistical significance.

3.3. Neurocognitive clusters and their association with clinical factors and plasma biomarkers

Cluster analysis resulted in three distinct subgroups (Fig. 1). Discriminant function analyses revealed two discriminant functions. The first accounted for 70.2% of the variability and the second accounted for 29.8% of the variance among the three subgroups. The domain deficit scores accurately classified 94.7% of the participants into one of the three selected clusters.

The first cluster was characterized as *Unimpaired* due to uniformly low (within normative expectations) deficit scores across all domains. The second cluster was characterized as *Learning/Recall* impairment due to isolated deficits in learning and delayed recall. The third cluster was characterized as *Dysexecutive/Slow* due to prominent deficits relative to the other two groups in executive function, working memory and speed-dependent domains (processing speed, motor), with milder learning and recall deficits relative to the *Learning/Recall* cluster. Verbal fluency

Table 2
Neurocognition by HIV serostatus.

	PWOH	PWH	*p*	*d*
T-scores				
Global	49.9 (6.0)	47.7 (5.1)	.007	−0.38
Verbal fluency	50.8 (8.4)	50.2 (7.7)	.599	−0.07
Executive function	49.8 (7.5)	47.7 (7.1)	.040	−0.29
Processing speed	52.5 (7.8)	48.9 (7.2)	.001	−0.48
Learning	45.5 (8.5)	43.8 (7.9)	.142	−0.21
Delayed recall	46.9 (8.3)	45.2 (8.3)	.152	−0.20
Working memory	50.2 (8.8)	46.9 (8.5)	.007	−0.38
Motor	50.8 (10.1)	49.4 (9.0)	.320	−0.14
Deficit scores				
Global	0.26 (0.29)	0.36 (0.36)	.042	0.29
Verbal fluency	0.21 (0.40)	0.21 (0.35)	.922	0.01
Executive function	0.23 (0.38)	0.33 (0.47)	.091	0.24
Processing speed	0.13 (0.34)	0.26 (0.45)	.026	0.32
Learning	0.49 (0.73)	0.59 (0.92)	.395	0.12
Delayed recall	0.39 (0.63)	0.51 (0.82)	.220	0.17
Working memory	0.30 (0.55)	0.51 (0.73)	.020	0.33
Motor	0.26 (0.64)	0.27 (0.64)	.948	0.01

Note. Values presented as mean (SD).

Table 3
Vascular and inflammation biomarkers by HIV serostatus.

	PWOH	PWH	*p*	*d*
Vascular biomarkers				
Vascular composite z	−0.10 (0.71)	0.12 (0.74)	.025	0.32
ICAM-1 z	−0.07 (1.03)	0.14 (0.92)	.144	0.21
VCAM-1 z	−0.22 (0.85)	0.28 (1.12)	<.001	0.52
suPAR z	−0.03 (0.96)	−0.05 (0.99)	.895	0.02
Inflammation biomarkers				
Inflammation composite z	−0.21 (0.68)	0.26 (0.67)	<.001	0.68
IL-6 z	−0.09 (1.02)	0.15 (0.98)	.093	0.24
CXCL10/IP-10 z	−0.28 (0.84)	0.42 (0.97)	<.001	0.78
CCL2/MCP-1 z	−0.25 (0.98)	0.20 (0.83)	<.001	0.49

Note. Values presented as mean (SD). Biomarker values were log-transformed and standardized for statistical testing and Cohen's *d* estimates.

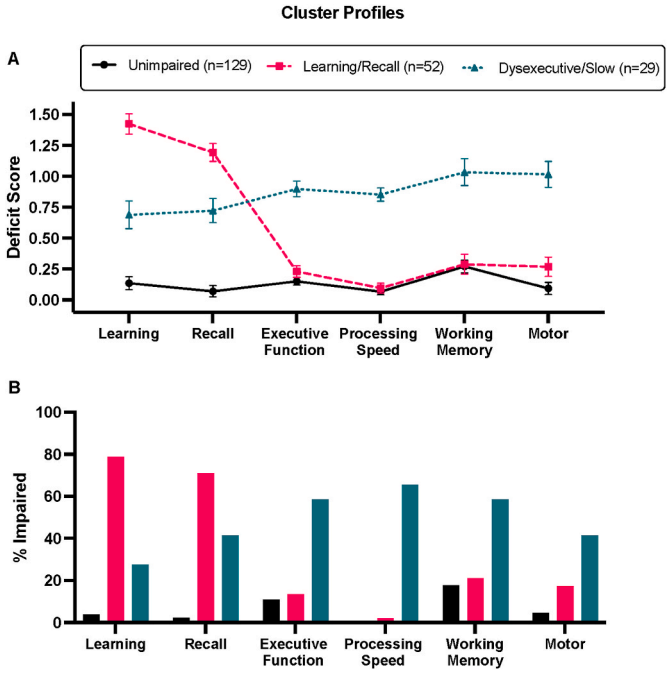

Fig. 1. Neurocognitive cluster profiles by deficit scores (panel A) and rate of impairment (i.e., deficit score>0.5; panel B). Cluster analysis revealed three distinct cognitive subtypes: *Unimpaired* (n = 129), *Learning/Recall* (n = 52), and *Dysexecutive/Slow* (n = 29).

deficit scores did not improve cluster segregation (verbal fluency R^2 contribution = 0.038; other domains [R^2 range: 0.22 to 0.51]) and therefore the final cluster solution did not incorporate verbal fluency deficit scores. Of the 210 participants in the present study sample, 129 (61%) were *Unimpaired*, 52 (25%) were *Learning/Recall*, and 29 (14%) were *Dysexecutive/Slow*.

3.4. Neurocognitive cluster group characteristics

Table 4 presents characteristics by cluster group in the whole sample. The proportion of HIV + individuals was significantly higher in the *Dysexecutive/Slow* deficit cluster (59%) relative to *Unimpaired* (35%; p = .019), though neither of these proportions differed significantly relative to the proportion of HIV+ in *Learning/Recall* (42%; *ps* = 0.158 and 0.352, respectively). Relative to *Unimpaired*, *Dysexecutive/Slow* exhibited significantly higher rates of hypertension, hyperlipidemia, and lifetime MDD (*ps* < .05) and increased central obesity (i.e., higher midwaist circumference; p < .05). *Dysexecutive/Slow* also exhibited higher rates of lifetime MDD and increased central obesity relative to *Learning/Recall* (*ps* < .05).

Table 4
Sample characteristics by neurocognitive cluster.

N = 210	Unimpaired (n = 129)	Learning/ Recall (n = 52)	Dysexecutive/ Slow (n = 29)	Pair-wise
	(a)	(b)	(c)	
Proportion PWH, n (%)	45 (34.9%)	22 (42.3%)	17 (58.6%)	c>a*
Demographics				
Age (years), mean (SD)	43.5 (14.7)	42.2 (14.7)	42.2 (14.7)	–
Sex (male), n (%)	90 (69.8%)	35 (67.3%)	21 (72.4%)	–
Education (years), mean (SD)	14.2 (2.2)	14.7 (2.5)	13.2 (2.2)	c<a*, b**
WRAT4, mean (SD)	104.8 (13.5)	103.2 (11.9)	102.2 (13.5)	–
Race/ethnicity				–
White, n (%)	74 (57.4%)	27 (51.9%)	17 (58.6%)	
Black, n (%)	22 (17.1%)	4 (7.7%)	3 (10.3%)	
Hispanic, n (%)	26 (20.2%)	14 (26.9%)	8 (27.6%)	
Asian, n (%)	3 (2.3%)	4 (7.7%)	0 (0.0%)	
Other, n (%)	4 (3.1%)	3 (5.8%)	1 (3.5%)	
Cardiometabolic Risk				
Body mass index, mean (SD)	27.9 (6.2)	27.7 (5.6)	28.9 (5.0)	–
Midwaist Circumference (cm), mean (SD)[a]	96.3 (15.5)	92.6 (15.7)	105.5 (16.6)	c>a*, b**
Diabetes, n (%)	5 (3.9%)	4 (7.7%)	1 (3.5%)	–
Hypertension, n (%)	21 (16.3%)	10 (19.2%)	10 (34.5%)	c>a*
Hyperlipidemia, n (%)	20 (15.5%)	8 (15.4%)	10 (34.5%)	c>a*, b
Ever smoker, n (%)[b]	91 (70.5%)	37 (72.6%)	20 (71.4%)	–
Current smoker, n (%)[c]	43 (34.1%)	16 (31.4%)	10 (38.6%)	–
Neuropsychiatric characteristics				
Lifetime Major Depressive Disorder, n (%)	38 (29.5%)	15 (28.9%)	16 (55.2%)	c>a**, b*
Current Major Depressive Disorder, n (%)[d]	9 (7.0%)	0 (0.0%)	3 (10.7%)	b<a, c*
Beck Depression Inventory-II, median [IQR]	11.0 [3.0, 11.0]	5.0 [1.0, 9.5]	10.0 [0.0, 16.5]	
Lifetime alcohol use disorder, n (%)	42 (32.6%)	25 (48.1%)	12 (41.4%)	–
Lifetime cannabis use disorder, n (%)	31 (24.0%)	11 (21.2%)	9 (31.0%)	–
Lifetime methamphetamine use disorder, n (%)	33 (25.6%)	14 (26.9%)	7 (24.1%)	–

Note. ART = antiretroviral therapy; WRAT4 = Wide-Range Achievement Test, Reading subtest.
**p < .01, *p < .05.
[a] N = 241.
[b] N = 208.
[c] N = 203.
[d] Current indicates meeting diagnostic criteria within the last 30 days.

In the HIV + group, with regard to HIV disease characteristics, *Learning/Recall* had a shorter estimated duration of HIV infection (median = 6.7 years) vs. *Dysexecutive/Slow* (median = 15.4 years, p = .005) and vs. *Unimpaired* (median = 10.7 years, p = .048). Duration of current ART regimen was significantly longer in *Unimpaired* (median = 18.8 months) vs. *Learning/Recall* (median = 9.8 months, p < .001) and vs. *Dysexecutive/Slow* (median = 8.1 months, p = .037). Conversely, cumulative lifetime exposure to ART was significantly longer in *Dysexecutive/Slow* (median = 105.2 months) vs. *Unimpaired* (median = 54.5

months, $p = .036$) and vs. *Learning/Recall* (median = 35.6 months, $p = .022$).

Cluster group differences in vascular and inflammation z-scores are displayed in Fig. 2. In the full sample, *Dysexecutive/Slow* exhibited significantly higher biomarker composite z-scores vs. *Unimpaired* (vascular: $d = 0.56$, $p = .007$; inflammation: $d = 0.52$, $p = .013$) and vs. *Learning/Recall* (vascular: $d = 0.55$, $p = .019$; inflammation: $d = 0.53$, $p = .024$), whereas biomarker composite z-scores did not differ between *Unimpaired* and *Learning/Recall* (vascular: $d = 0.01$, $p = .954$; inflammation: $d = 0.01$, $p = .951$). In the HIV + group, a similar pattern emerged for the vascular composite z-score: *Dysexecutive/Slow* had significantly higher z-scores vs. *Unimpaired* ($d = 0.71$, $p = .014$) and vs. *Learning/Recall* ($d = 0.69$, $p = .033$). Cluster group differences in inflammation did not reach statistical significance in the HIV + stratum, although *Dysexecutive/Slow* trended toward higher inflammation z-scores vs. *Learning/Recall* ($d = 0.54$, $p = .094$). In the HIV- group, cluster groups did not significantly differ on either vascular ($ps > .441$) or inflammation z-scores ($ps > .203$).

3.5. Interactive effects of HIV and plasma biomarkers on neurocognition

The domains of executive function, processing speed, working memory, and motor were selected for follow-up analysis given the observed associations between elevated biomarker composite z-scores and *Dysexecutive/Slow* group membership. Univariably, higher vascular z-scores correlated with lower executive function ($r = -.21$, $p = .002$, FDR-adjusted $p = .007$), processing speed ($r = -0.17$, $p = .014$, FDR-adjusted $p = .029$), and working memory T-scores ($r = -0.23$, $p < .001$, FDR-adjusted $p = .007$). Adjusting for covariates (i.e., hypertension, hyperlipidemia, lifetime MDD, BDI-II, smoking [ever], and WRAT-4), multiple regression results indicated significant interaction effects of HIV and vascular z-scores (Fig. 3) for each of the three domains with significant univariable associations (executive function: b = −3.08, β = −0.23, $p = .022$; processing speed: b = −2.96, β = −0.21, $p = .046$; working memory: b = −3.77, β = −0.23, $p = .021$). Specifically, higher vascular z-scores significantly related to lower T-scores in HIV + individuals (executive function: $b = -3.18$, β = −0.31, $p = .002$; processing speed: $b = -2.79$, β = −0.26, $p = .013$; working memory: $b = -4.15$, β = −0.34, $p < .001$), yet did not significantly relate to T-scores in HIV- individuals (executive function: $b = -0.10$, β = −0.01, $p = .915$; processing speed: $b = 0.17$, β = 0.02, $p = .860$; working memory: $b = -0.38$, β = −0.03, $p = .722$). Results remained unchanged when additionally adjusting for inflammation z-scores.

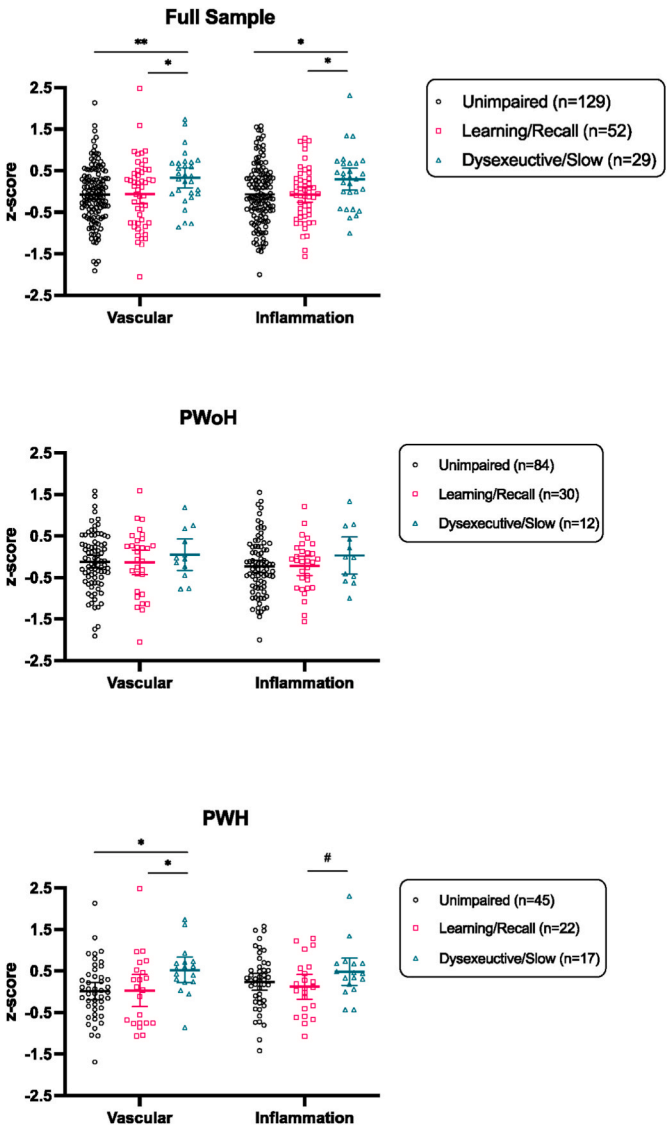

Fig. 2. Vascular and inflammation biomarkers by cluster group (A: full sample; B: PWoH; C: PWH). #$p < .10$, *$p < .05$, **$p < .01$.

Univariably, higher inflammation composite z-scores only correlated with lower motor T-scores ($r = -0.17$, $p = .012$, FDR-adjusted $p = .029$). Inflammation z-scores did not significantly interact with HIV serostatus to predict motor T-scores ($b = 0.77$, β = 0.04, $p = .706$); however, higher inflammation z-scores exhibited a significant, independent main effect on lower motor T-scores ($b = -2.07$, β = −0.15, $p = .041$).

To determine whether any individual vascular biomarker (i.e., VCAM-1, ICAM-1, and uPAR) was driving the associations between the vascular composite score and significant domains (executive functions, processing speed, working memory) in the HIV + group, we removed one biomarker at a time from the vascular composite and re-examined relationships with executive functions, processing speed, and working memory T-scores in the HIV + group, controlling for the FDR. All three variations of the vascular composite (i.e., VCAM-1/ICAM-1, VCAM-1/uPAR, and ICAM-1/uPAR) were significantly associated with executive function (*rs* = −0.31, −0.32, and −0.34, respectively; FDR-adjusted *ps* < 0.01) and working memory (*rs* = -0.40, −0.37, and −0.36, respectively; FDR-adjusted *ps* < 0.01). Only composites that included VCAM-1 (i.e., VCAM-1/ICAM-1 and VCAM-1/uPAR) were significantly associated with processing speed (*rs* = -0.27 and −0.34, respectively; *ps* = 0.028 and 0.004). To determine whether any of the individual vascular biomarkers were uniquely associated with these domain T-scores, we entered the three vascular biomarkers into individual regression models with executive functioning, processing speed, and working memory T-scores as outcome variables, and controlling for relevant covariates and HIV disease/treatment characteristics. In these multiple regression models, VCAM-1 was the only individual biomarker that remained significantly associated with worse performance in all three domains (β range: 0.36 to −0.27, *ps* < 0.05) and uPAR was marginally associated with worse working memory (β = −0.25, $p = .053$).

A similar series of analyses was conducted for the inflammation composite and the motor domain but in the whole sample, given the lack of a significant HIV by inflammation composite interaction. In the whole sample, only inflammation composites that included IL-6 (i.e., IL-6/[CXCL10/IP-10] and IL-6/[CCL2/MCP-1]) were significantly associated with lower motor T-scores (*rs* = −0.16 and −0.20; FDR-adjusted *ps* = 0.031 and 0.008). None of the individual biomarkers was significantly associated with motor performance in the multiple regression model (*ps* > 0.05).

4. Discussion

The present study empirically-derived profiles of neurocognitive deficits in virally suppressed PWH and PWoH, and examined biomarker evidence of systemic inflammation and vascular processes (i.e.,

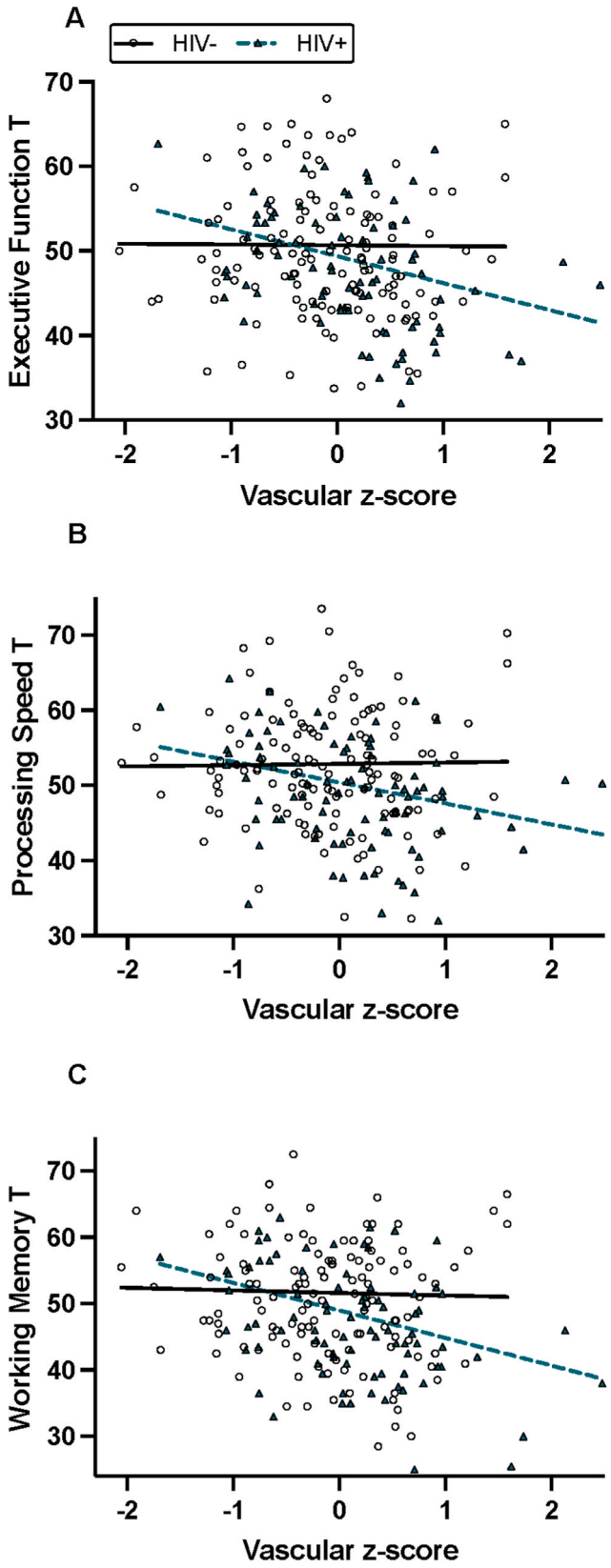

Fig. 3. Interactive effects of HIV and vascular z-scores on neurocognition (A: executive function; B: processing speed; C: working memory). Higher vascular biomarker levels were selectively associated with worse cognition in PWH, but not PWoH.

endothelial dysfunction and vascular permeability) as underlying risk factors contributing to these profiles. Using hierarchical cluster analyses, three distinct neurocognitive subgroups emerged: one with no to minimal deficits across all domains ("Unimpaired"; 61% of the sample), one with relatively isolated and prominent deficits in learning and memory ("Learning/Memory"; 25% of the sample), and one with global deficits across domains but, relative to the other two groups, this group had disproportionate impairment in executive functions, processing speed, working memory, and motor skills ("Dysexecutive/Slow" (14% of the sample). Notably, Dysexecutive/Slow membership was more prevalent among PWH, whereas the prevalence of Learning/Memory membership was similar across PWH and PWoH. PWH exhibited elevations in vascular biomarkers, which in turn showed a selective association with Dysexecutive/Slow group membership among PWH. This association between circulating vascular biomarkers and HIV-related neurocognitive performance was reproduced (specifically executive functions, processing speed, and working memory T-scores) in linear regression models that controlled for traditional cardiovascular risk factors (e.g., hypertension, hyperlipidemia), psychiatric comorbidities (e.g., MDD), and HIV disease and treatment characteristics. Furthermore, the link between the vascular biomarker composite and the HIV-related Dysexecutive/Slow phenotype was robust to the inflammation composite, which was also elevated in PWH relative to PWoH but only weakly associated, regardless of HIV status, with worse motor performance. Collectively, these findings support evidence of ongoing inflammation and associated vascular mechanisms in the context of viral suppression (Deeks et al., 2015), and highlight the potential unique role of endothelial dysfunction and vascular permeability as mechanisms underlying a cluster of deficits characterized by executive dysfunction, cognitive slowing, and poor working memory in virally suppressed PWH.

The deficit profiles observed in our study as well as the proportions of PWH with each deficit profile are consistent with those observed in another recent study by our group that was conducted in an independent sample of older (age 50+ years) PWH and PWoH using latent class analyses (Pasipanodya et al., 2019). Interestingly, similar numbers and patterns of deficit profiles have been observed in other clinical samples of PWoH with similar heterogeneity of neurocognitive deficits and targeted brain regions (e.g., non-demented Parkinson's disease (Brennan et al., 2017); mild cognitive impairment (Eppig et al., 2017)). While the number and pattern of deficit profiles may be similar across clinical populations, the risk factors underlying each profile may differ depending on the clinical population of interest and characteristics of the sample. In the current study, medical and psychiatric risk factors associated with the multidomain *Dysexecutive/Slow* deficit profile included HIV disease, hypertension, hyperlipidemia, increased central adiposity, and LT MDD, and with regard to HIV disease and treatment characteristics, risk factors included longer duration of HIV disease and greater cumulative lifetime exposure to ART. The increased cardiovascular disease risk coupled with greater ART exposure in the Dysexecutive/Slow group is salient given that HIV treatment, particularly PI-based regimens (Echecopar-Sabogal et al., 2017; Graham, 2000), has been linked to cardiometabolic dysfunction (e.g., dyslipidemia), which is consistently associated with NCI in other studies of ART-treated PWH (Ciccarelli et al., 2014; Sacktor et al., 2016), including a multi-domain deficit profile (Pasipanodya et al., 2019). The elevated central adiposity, but not BMI, in the *Dysexecutive/Slow* group is also consistent with a prior study demonstrating central adiposity as a stronger predictor of neurocognitive impairment than BMI in PWH (McCutchan et al., 2012).

A primary objective of this study was to determine and differentiate the contributions of inflammation and vascular biomarkers to neurocognitive deficit profiles and performance in virally suppressed PWH. The inflammatory and vascular composites were strongly correlated and both were elevated in our sample of virally suppressed PWH relative to PWoH, consistent with prior studies (Anderson et al., 2020; Hoenigl et al., 2019; Melendez et al., 2008; Montoya et al., 2019). Significant

elevations with regard to individual biomarkers were found for VCAM-1 (within the vascular composite) and chemokines CXCL10/IP-10 and CCL2/MCP-1 (within the inflammation composite). The contributions of vascular and inflammatory processes to NCI in this study were profile- and domain-specific. In concert with the higher cardiometabolic disease burden observed in the *Dysexecutive/Slow* group, the vascular composite was uniquely associated with the domains of executive function, working memory, and processing speed, which further supports a potential "vascular" profile of neurocognitive deficits in PWH. While deficits in executive function, working memory, and processing speed are frequent in HAND (Heaton et al., 2011; Woods et al., 2009), these domains are also commonly affected in vascular cognitive impairment (Sachdev et al., 2004; Vasquez and Zakzanis, 2015), and rely on the prefrontal cortex and its extensive connections with other cortical and subcortical brain regions. As such, these domains are highly vulnerable to white matter damage in PWH (Watson et al., 2017), consistent with imaging studies conducted in other clinical (e.g., neurodegenerative) and non-clinical (e.g., normal aging) samples (Bettcher et al., 2016; Tartaglia et al., 2012).

Although our data do not directly address the molecular cross-talk between viral, immune, and vascular processes, our results provide preliminary insight into specific vascular mechanisms in ART-treated PWH that may lead to this particular profile of neurocognitive deficits. The three soluble biomarkers included in our vascular composite, VCAM-1, ICAM-1, and uPAR, were selected as indicators of endothelial dysfunction that have shown previous associations with HIV (Graham et al., 2013; Sidenius et al., 2000) as well as inflammation, atherosclerosis and CVD (e.g., (Hoenigl et al., 2019; Kirkegaard-Klitbo et al., 2017; Melendez et al., 2008). VCAM-1 and ICAM-1 are released in response to inflammation (Libby et al., 2002) and facilitate the adhesion and migration of immune and viral factors into and across the vascular endothelium (Kong et al., 2018; Wong et al., 1999). While VCAM-1 is exclusively expressed on endothelial cells, ICAM-1 is also expressed on leukocytes, astrocytes, and microglial cells (Müller, 2019). uPAR is a glycoprotein expressed on endothelial cells, in addition to immune (e.g., monocytes/macrophages) and neuronal cells, that facilitates increased vascular permeability, immune cell trafficking, and mitogenic activity, leading to endothelial dysfunction. Blood levels of soluble uPAR are increased in untreated PWH (Schneider et al., 2007), reduced upon ART initiation (Ostrowski et al., 2006), and almost normalized with sustained ART (Ostrowski et al., 2004). The associations between the vascular biomarker composite and neurocognitive T-scores were stronger than those of individual biomarkers alone suggesting that each may contribute uniquely to impairment. However, of the three vascular biomarkers, VCAM-1 was the only individual vascular biomarker to emerge as a significant predictor of all three neurocognitive domains when controlling for vascular risk factors and other relevant covariates. It was also the only vascular biomarker that was significantly elevated in our sample of virally suppressed PWH relative to PWoH. This is consistent with studies that have found persistent elevation in VCAM-1 but not ICAM-1 levels following ART and viral suppression (Calza et al., 2009; Papasavvas et al., 2008). Given its sensitivity to viral replication and potential for persistent elevations following prolonged ART, VCAM-1 may be a useful prognostic marker for CVD risk and related neurocognitive sequelae in both treated and untreated PWH.

Collectively these findings support the presence of persistent low-grade inflammation in PWH but highlight endothelial dysfunction as a key mechanism underlying NCI in treated PWH. In our study, inflammation was elevated in PWH relative to PWoH though only weakly associated, and regardless of HIV status, with worse performance in the motor skills domain. Other studies conducted in PWH have also failed to find associations between persistent inflammation and NCI in the context of treated and well-controlled HIV (Pedersen et al., 2013). Persistent immune activation and inflammation in PWH, while present, may not be a primary or direct contributor to NCI in the context of treated and well-controlled HIV disease. One exception may be the selective impact of persistent inflammation on motor deficits, a domain that historically has been most impacted among PWH with chronic disease and/or a history of immunosuppression (Baldewicz et al., 2004; Woods et al., 2009). This inflammation-motor link replicates another study in virally suppressed PWH that was conducted in a different sample by investigators from our group (Montoya et al., 2019). Specifically, they found that inflammation, as indexed by a composite burden score that included levels of IL-6, CCL2/MCP-1, sCD14, TNF-a and d-dimer, was associated with poorer performance within the motor skills domain but not other domains. Our weaker results with regard to inflammation may be due differences in individual biomarkers or our approach to constructing composites (i.e., as an average of biomarkers vs. number of elevated biomarkers [$\geq$75th percentile]). Regardless, persistent inflammation may continue to impact NCI in other domains indirectly via its adverse effects on the vascular system and non-HIV-associated complications.

This study is among the first to directly compare systemic vascular and inflammatory biomarkers in relation to empirically-derived profiles of neurocognition in a well-characterized cohort of virally-suppressed PWH. However, we acknowledge several limitations. The cross-sectional nature of our data limits our ability to identify temporal patterns regarding the development of inflammation, endothelial dysfunction, and neurocognitive deficits in the context of chronic HIV disease and treatment. Thus, a future analysis that leverages longitudinal data can help address whether subsequent reductions in vascular biomarkers track with improvements in neurocognition among PWH. The current study also did not have access to data for medications that treat cardiovascular conditions, including statin use. Although vascular biomarkers can still show elevations with statin use (Mosepele et al., 2018), prior work has shown that PWH with untreated cardiovascular risk performed worse than those with treated cardiovascular risk on multiple neurocognitive domains, including processing speed, learning/memory, and executive functioning (Foley et al., 2010). It is compelling to hypothesize that the elevated vascular biomarker levels in the *Dysexecutive/Slow* group reflect particular vulnerabilities in fronto-striatal and fronto-parietal networks, possibly in white matter tracts sensitive to neurovascular dysfunction and HIV disease, yet our data do not include direct measurements of structural or functional integrity of specific brain regions (e.g., structural MRI, diffusion tensor imaging, cerebral blood flow). Although similar numbers of clusters/classes and patterns of NC domain impairment have been observed across clinical and non-clinical samples and statistical methods (Brennan et al., 2017; Eppig et al., 2017; Pasipanodya et al., 2019), it is possible that cluster analyses in larger independent HIV samples may reveal other clinically relevant neurocognitive profiles. Last, the PWoH comparison group cannot be interpreted as absolute 'controls' given their medical and neuropsychiatric backgrounds – however, these background factors more closely resemble the PWH group, which strengthens our observations of HIV-specific relationships between vascular biomarkers and neurocognition.

The identification of plasma biomarkers that sensitively track with particular neurocognitive deficits and medical profiles will inform efforts to improve neuroHIV clinical care through scalable assessments and tailored interventions. In the present study, our findings support the growing recognition for a vascular subtype of HIV-associated NCI that exhibits a profile of deficits in executive functions and speed-dependent tasks, similar to the classic presentation of vascular cognitive impairment. Our data also highlight endothelial dysfunction as a potential direct mechanism driving this deficit profile, which underscores the importance of neurovascular pathology in the context of viral suppression. Taken together, this vascular NCI subgroup of PWH may benefit the most from interventions that target the neurovascular unit directly (e.g., pharmacologic) and indirectly (e.g., modifiable lifestyle factors), which will improve early detection and treatment of NCI, as well as preventing further decline, particularly as the HIV population grows older.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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