Higher Peripheral Monocyte Activation Markers Are Associated With Smaller Frontal and Temporal Cortical Volumes in Women With HIV

Asante R. Kamkwalala, PhD,[a] Xuzhi Wang, PhD,[b] Pauline M. Maki, PhD,[c] Dionna W. Williams, PhD,[d,e] Victor G. Valcour, MD, PhD,[f] Alexandra Damron,[a] Phyllis C. Tien, MD,[g,h] Kathleen M. Weber, MS,[i] Mardge H. Cohen, MD,[i] Erin E. Sundermann, PhD,[j] Vanessa J. Meyer, PhD,[c] Deborah M. Little, PhD,[k] Yanxun Xu, PhD,[b,l] and Leah H. Rubin, PhD, MPH[a,m,n]

Background: Persistent inflammation is a life-long complication of HIV infection, even in virally suppressed individuals. Elevated plasma concentrations of soluble(s) CD14 and CD163 have been established as biomarkers of chronic inflammation, conferring higher risk for cognitive, neurovascular, and structural abnormalities.

Methods: Structural magnetic resonance imaging (frontal and temporal regions) as well as plasma inflammatory biomarkers of monocyte activation (sCD14 and sCD163), general inflammation (plasma C-reactive protein, interleukin[IL]-6), and gut microbial translocation (plasma intestinal fatty acid–binding protein) were available on 38 women (25 with HIV) from the Chicago Women's Interagency HIV Study site. Partial least-squares models adjusting for relevant covariates (eg, age, education, and race) were conducted to evaluate the relationship between inflammatory biomarkers and brain volume in the overall sample and among women with HIV (WWH).

Results: In the total sample, higher plasma sCD14 was associated with smaller volumes in multiple frontal and temporal lobe regions. In the WWH-only sample, sCD163 was associated with smaller volumes only in one region of the left frontal lobe. C-reactive protein, IL-6, and intestinal fatty acid–binding protein were not associated with brain volumes for either group of women.

Conclusions: Of the inflammatory monocyte markers evaluated, sCD14 was associated with smaller frontal and temporal cortical volume in the overall and WWH-only samples, while plasma sCD163 was only associated with smaller left caudal middle frontal gyrus in the WWH-only group. Validating these monocyte proteins as neurological biomarkers of structural brain deficits in a larger sample is critical for understanding HIV-associated neurobiological complications.

Key Words: CD14, CD163, monocyte, brain volume, HIV, women

(*J Acquir Immune Defic Syndr* 2020;84:54–59)

INTRODUCTION

Overactivation of inflammatory pathways is an ongoing medical challenge for individuals living with chronic HIV infection.[1–4] As a result of infection, peripheral macrophages and monocytes activate to initiate an inflammatory response to the toxic and foreign viral particles, releasing inflammatory proteins and cytokines and ultimately contributing to a phenotype of persistent inflammation known to be associated with chronic HIV infection.[5,6] Compared with nonspecific markers such as IL-6 or C-reactive protein (CRP),

Received for publication October 18, 2019; accepted December 13, 2019.

From the Departments of [a]Neurology; [b]Applied Mathematics and Statistics, Johns Hopkins University, Baltimore, MD; [c]Departments of Psychiatry and Psychology, University of Illinois at Chicago, Chicago, IL; [d]Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine, Baltimore, MD; [e]Division of Clinical Pharmacology, Johns Hopkins University School of Medicine, Baltimore, MD; [f]Department of Neurology, Memory and Aging Center, University of California, San Francisco, CA; [g]Department of Medicine, University of California, San Francisco, San Francisco, CA; [h]Department of Veterans Affairs Medical Center, San Francisco, CA; [i]CORE Center, Cook County Health and Hektoen Institute of Medicine, Chicago, IL; [j]Department of Psychiatry, University of California San Diego School of Medicine, La Jolla, CA; [k]Department of Psychiatry and Behavioral Sciences, University of Texas Health Science Center at Houston, Houston, TX; [l]Division of Biostatistics and Bioinformatics at The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD; [m]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; and [n]Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD.

Data in this manuscript were collected by the Chicago site of the Women's Interagency HIV study (WIHS) and are funded by National Institute of Allergy and Infectious Diseases (NIAID) Grant U01 A1034993 (PI: M.H.C., MD) and cofunded by National Cancer Institute and National Institute of Drug Abuse. L.H.R.'s effort was supported by Grant number K01MH098798 from the National Institute of Mental Health (NIMH), Grant number K12HD055892 from the National Institute of Child Health and Human Development (NICHD), and National Institutes of Health Office of Research on Women's Health (ORWH), and Grant number P30MH075773 from the National Institute of Mental Health (NIMH).This grant was also supported by the Chicago Developmental Center for AIDS Research (D-CFAR), an NIH-funded program (P30 AI 082151), which is supported by the following NIH Institutes and Centers (NIAID, NCI, NIMH, NIDA, NICHD, NHLBI, and NCCAM). V.J.M.'s effort on this project was supported by the National Institute on Drug Abuse (F31DA028573). E.E.S.'s effort on this project was supported by the National Institute of Mental Health (F31MH083537). D.W.W. effort was supported by R00DA044838.

The authors have no conflicts of interest to disclose.

A.R.K., X.W., P.M.M., Y.X., and L.H.R. contributed equally.

Correspondence to: Leah H. Rubin, PhD, MPH, Department of Neurology, Johns Hopkins University School of Medicine, 600 N, Wolfe Street, Meyer 6-113, Baltimore, MD 21287-7613 (e-mail: lrubin1@jhmi.edu).

myeloid-specific derived markers of inflammation, specifically soluble CD14 (sCD14) and CD163 (sCD163) are associated with numerous comorbidities that can increase risk for mortality in people with HIV (PWH), such as intestinal dysfunction,[7–9] cardiovascular complications,[10,11] and neurological/cognitive impairments.[12–14]

Two myeloid-specific immune proteins, sCD14 and sCD163, are closely associated with the initiation and persistence of inflammation in PWH. In the early stages of HIV infection, compromise of immune cells in the intestinal tract and gut can allow for microbes to cross gastrointestinal mucosal membranes unimpeded into peripheral circulation.[15,16] These translocated microbes release liposaccharides that bind to membrane-bound CD14 and CD163 receptors on monocytes, activating these monocytes and initiating an immune response, cleaving the CD14 and CD163 proteins from the cell surface into soluble forms into the plasma.[17–21]

These biomarkers of myeloid-specific inflammatory activation can be readily detected in plasma, but also in cerebrospinal fluid,[13,22] indicating that they have the potential to negatively affect the central nervous system (CNS). Indeed, elevated concentrations of sCD14 and sCD163 have previously been associated with a number of negative neurological outcomes in PWH, such as poorer neurocognitive performance in domains of memory, processing speed, and executive function,[23,24] lower total gray matter volumes,[25] decreases in white matter fractional anisotropy,[26] and increased risk of stroke and neurovascular comorbidities.[27–29] In addition, the effects of inflammatory biomarkers on brain structure in the frontal and temporal cortices may be particularly salient to women with HIV (WWH) because it has been demonstrated that inflammation-related neural consequences are more severe in WWH compared to men with HIV.[23,30,31] The current study was designed to evaluate associations between plasma biomarkers of monocyte activation and frontal and temporal brain volumes in a sample of WWH and HIV-seronegative women. We hypothesized that higher peripheral levels of monocyte activation markers (sCD14 and sCD163) would be more strongly associated with smaller medial temporal and frontal lobe brain volumes, as compared to nonspecific inflammatory markers (IL-6 and CRP) and gastrointestinal mucosa damage intestinal fatty acid–binding protein (I-FABP) in WWH.

METHODS

Participants

Participants were enrolled in the Chicago Women's Interagency HIV Study Consortium during semiannual visits in 2010–2011. One hundred ninety-nine women were approached by Women's Interagency HIV Study staff for participation based on the following inclusion criteria: English speaking, age 21–60 years, and completion of at least 8 years of formal education. Eighty-four (84) women completed a phone screen with study personnel, and 10 were ineligible due to the following exclusion criteria: history of dementia (1), uncontrolled diabetes (2), visual impairment (1), current pregnancy (1), self-reported psychosis diagnoses (2), current hospitalization (1), and current psychiatric medication with known CNS effects (2). An additional seven (7) women were excluded due to magnetic resonance imaging (MRI) exclusion criteria: metal in the body (5); claustrophobia (1); and over 250 pounds (1). Of the remaining 67 women, 62 were scheduled for a visit to the University of Illinois at Chicago and consented to participation. After informed consent, an additional six (6) women voluntarily withdrew consent, and a total of 56 women (39 WWH) completed the imaging protocol. Of these 56 women, 38 women (25 WWH) had peripheral inflammatory marker levels available and were included in the present analysis.

Laboratory Measurements

sCD14, sCD163, and I-FABP were measured in frozen plasma specimens stored at −70°C using commercially available enzyme-linked immunosorbent assays (ELISA) [sCD14 and sCD163: Quantikine ELISA kit (R&D Systems, Minneapolis, MN) and I-FABP: ELISA kit (Hycult Biotech, Uden, Netherlands)]. CRP and IL-6 were measured in frozen sera stored at −70°C using ELISA [CRP: BNII nephelometer (Dade Behring, Deerfield, IL); IL-6: Quantikine HS Human IL-6 Immunoassay kit (R&D Systems)]. The limits of detection were as follows: sCD14 = 125 pg/mL, sCD163 = 0.613 ng/mL, I-FABP = 6.21 pg/mL, CRP = 0.17 mg/L, and hsIL-6 = 0.11 pg/mL. All tests were conducted according to manufacturers' instructions. Coefficient variances (CVs) were <10% or were repeated. Sensitivities for these assays are listed on R&D Systems' (the manufacturer's) assay inserts and were not specifically examined. Positive controls included a quality control sample purchased from the manufacturer and included a high, medium, and low concentration of each analyte and were run in duplicate. The quality control catalogue numbers for each cytokine were as follows: sCD14 (#QC20), sCD163 (#QC61), I-FABP (#QC213), CRP (OQDB13), and hsIL-6 (#QC41).

Psychological Profile Assessments

Incidence and severity of mood symptoms (depression and stress) were assessed through 3 validated self-report measures, collected on all participants before their first MRI scan. The Perceived Stress Scale (PSS-10) assesses subjective appraisal of stressful life events,[32] the PTSD Checklist-Civilian is a self-report measure of DSM-IV PTSD symptoms,[33] and the Center for Epidemiological Studies–Depression Scale screens for symptoms of depression.[34]

Structural MRI

MRI scans were performed using a General Electric 3.0-Tesla Signa HDx scanner (General Electric Healthcare, Waukesha, WI). Structural imaging was acquired using a T1-weighted 3-dimensional inversion recovered fast-spoiled gradient echo sequence [repetition time (TR)/echo time (TE)/inversion recovery (IR)] = 13.8/4.3/300, flip angle = 25 degrees, 120 slices. FreeSurfer (version 5.1.0 available at http://surfer.nmr.mgh.harvard.edu/) was used to extract

volumetric data for each participant. The a priori regions of interested were the medial temporal lobes, frontal cortex, and insula, given their roles in neuropsychiatric function. In the medial temporal lobes, we extracted volumetric data in the hippocampus, parahippocampal region (parahippocampal gyri and entorhinal cortex), and amygdala. In the frontal lobe, we extracted volumetric data in the superior frontal, middle frontal (rostral and caudal), and inferior frontal gyri (pars opercularis, pars triangularis, and pars orbitalis), orbital frontal cortex (lateral and medial), and anterior cingulate (rostral and caudal). Automated volumetry in subcortical structures has been previously been shown to be reliable and valid in PWH.[35] Brain volumes were corrected for the total intracranial volume, derived from the sum of gray matter, white matter, and cerebral spinal fluid.[36,37] Specifically, all cortical volumes (mm^3) were divided by the total intracranial volume (mm^3) and multiplied by 1000. There were 6 outliers across all brain volumes of interest (<1% of the data), and these values were winsorized to be equivalent to the next highest/lowest volume within their respective groups.

Statistical Analysis

Before analysis, distributions for all predictors, outcomes, and covariates were examined. The distributions for all inflammatory markers were skewed and therefore log transformed. To address associations between inflammatory markers and cortical brain volume, we conducted 2 partial least-squares (PLS) regression analyses—one in the overall sample and one in WWH only. PLS was selected because this method effectively handles correlations between predictors (inflammatory markers) and outcomes (regional cortical brain volumes), multiple outcomes, and data in which the number of observations is smaller than the number of predictor variables. Both models controlled for age, years of education, race, body mass index, and depressive symptoms. The model in the overall sample also included HIV serostatus. In WWH-only analysis, the model also included CD4 nadir. Viral load was not included as a covariate because this variable was not related to levels of inflammatory markers. Significance was set at $P < 0.05$. All statistical analyses were conducted in R (version 3.6.1).

RESULTS

Participant Characteristics

Table 1 includes sociodemographic, clinical, and behavioral characteristics of the overall sample (n = 38) and WWH only (n = 25). WWH were not significantly different from the overall sample in terms of sociodemographic factors, with a similar age range, years of education, and racial breakdown. Baseline scores on the Wide Range Achievement Test reading subtest were also similar. WWH were more likely to be heavy smokers and slightly more likely to be heavy users of alcohol or marijuana relative to the overall sample. However, the percentage of participants endorsing crack, cocaine, and/or heroin use was not significantly different in the WWH only sample,

TABLE 1. Demographic and Clinical Characteristics for the Total Sample and for Women With HIV (WWH) Only

Variables	Total Sample (n = 38)	WWH Only (n = 25; 66%)
Sociodemographic factors, n (%)		
Age, M (SD)	43.6 (8.6)	43.9 (7.2)
WRAT-R, M (SD)	89.9 (16.8)	81.7 (18.2)
Years of education, M (SD)	12.3 (1.9)	12.1 (2.0)
Race/ethnicity		
African American	36 (95)	24 (96)
Caucasian	2 (5)	1 (4)
Risky health behaviors, n (%)		
Currently smoking	29 (76)	19 (76)
Recent* use		
Alcohol		
Abstainer	20 (53)	14 (56)
Not heavy	13 (32)	3 (28)
Heavy	5 (13)	8 (32)
Marijuana	8 (21)	3 (12)
Crack, cocaine, and/or heroin	3 (8)	3 (12)
Ever use		
Marijuana	23 (60)	17 (68)
Crack, cocaine, and/or heroin	24 (63)	16 (64)
Body mass index	25.4 (3.5)	25.1 (3.5)
Psychological profile, M (SD)		
Perceived Stress Scale (PSS-10)	15.5 (8.0)	17.0 (6.2)
Depressive symptoms (CES-D)	11.2 (6.2)	12.1 (6.3)
PTSD checklist-civilian version (PCL-C)	32.7 (13.7)	34.3 (10.9)
Clinical characteristics, n (%)		
Hepatitis C virus antibody (HCV)	10 (26)	7 (28)
Nadir CD4 count (cells/μL), M (SD)		309 (172)
CD4 count (cells/μL)		
>500		10 (40)
≥200 and ≤500		11 (44)
<200		2 (16)
Viral load [HIV RNA (cp/mL)]		
Undetectable		12 (48)
<10,000		9 (36)
≥10,000		4 (16)
Medication use + medication adherence		
No cART or cART+ <95% adherence		9 (36)
cART+ ≥95% adherence		16 (64)
Inflammatory markers, median (IQR)		
sCD14 (ng/mL)	1634.4 (818)	1844.5 (698)
sCD163 (ng/mL)	391.7 (402)	529.7 (508)
I-FABP (ng/mL)	614.8 (737)	674.5 (997)
CRP (mg/L)	1.5 (4.3)	1.4 (3.9)
IL-6 (mg/L)	1.2 (1)	1.3 (1)

Heavy alcohol use = >7 drinks per week or >4 drinks at a sitting; undetectable = <48 copies/mL.

*"Recent" refers to within 6 months of the most recent WIHS visit.

cART, combination antiretroviral therapy; IQR, interquartile range; WIHS, Women's Interagency HIV Study; WRAT-R, Wide Range Achievement Test Standard Score.

compared with the overall sample. WWH also had consistently higher scores on the Perceived Stress Scale, PTSD Checklist-Civilian, and Center for Epidemiological Studies–Depression Scale, relative to the overall sample. In the WWH, the majority (64%) were on stable combination antiretroviral therapy (reporting at least 95% adherence, determined through self-report), had a viral load of less than 10,000 copies/mL (84%) and a current CD4 count of at least 200 cells/μL (84%).

With respect to inflammatory markers, WWH had higher log plasma sCD163 ($P = 0.01$), sCD14 ($P = 0.02$), and I-FABP ($P = 0.04$) compared with HIV-uninfected women in the overall samples. There were no differences on IL-6 ($P = 0.12$) or CRP ($P = 0.69$). With respect to brain volumes, WWH compared with HIV-uninfected women in the overall sample only showed smaller volumes in the right amygdala ($P = 0.04$), left medial orbital frontal cortex ($P = 0.02$), and a trend-level decrease in volume of the right rostral anterior cingulate ($P = 0.08$).

Imaging Results

Standardized beta (β) coefficients and *P*-values for significant regions of interest (ROIs) from the PLS analyses are in Table 2.

Overall Sample

In the medial temporal cortex, higher plasma sCD14 levels were associated with smaller volumes in the left parahippocampal gyrus ($\beta = -0.53$, $P < 0.01$) and the left entorhinal cortex ($\beta = -0.55$, $P < 0.01$). In the frontal cortex, higher plasma sCD14 levels were associated with smaller volumes in the left rostral middle frontal gyrus ($\beta = -0.47$, $P < 0.05$) and right frontal gyrus (pars opercularis) ($P < 0.01$). sCD163, CRP, IL-6, and I-FABP were not significantly associated with cortical volumes in these regions.

WWH Only

Higher plasma sCD14 levels were associated with smaller volumes in the right inferior frontal gyrus ($\beta = -0.17$, $P < 0.05$), the right superior frontal gyrus ($\beta = -0.22$, $P < 0.05$), and the left superior frontal gyrus ($\beta = -0.21$, $P < 0.05$). In addition, higher plasma sCD163 levels were associated with smaller volumes in the left caudal middle frontal gyrus ($\beta = -0.21$, $P < 0.05$). No associations were seen with CRP, IL-6, and I-FABP.

TABLE 2. Associations Between Peripheral Inflammatory Markers and Cortical Brain Volume in the Total Sample of 38 Women and Among the 25 Women With HIV (WWH)

	Marker (β Coefficient)	
Region	**sCD14**	**sCD163**
Model 1 (total sample)		
Medial temporal region		
Left parahippocampal gyrus	−0.53**	
Left entorhinal cortex	−0.55**	
Frontal region		
Left rostral middle frontal gyrus	−0.47*	
Right inferior frontal gyrus (pars opercularis)	−0.39*	
Model 2 (WWH only)		
Frontal region		
Right inferior frontal gyrus (pars opercularis)	−0.17*	
Right superior frontal gyrus	−0.22*	
Left superior frontal gyrus	−0.21*	
Left caudal middle frontal gyrus		−0.17*

The model conducted in the overall sample adjusted for age, body mass index, depressive symptoms, years of education, HIV-serostatus, and race. Models conducted in the WWH adjusted for age, body mass index, depressive symptoms, years of education, and race. In Model 2, CD4 nadir was added.

**$P < 0.01$.

*$P < 0.05$.

β, standardized beta coefficient; s, soluble.

DISCUSSION

Our results showed that, in the whole sample, elevated plasma sCD14 was associated with significantly smaller volumes in multiple regions of the frontal and temporal lobes: left parahippocampal and entorhinal cortex in the temporal lobe, and left rostral middle gyrus and right inferior middle gyrus in the frontal lobes. Elevated plasma levels of sCD163 was only associated with smaller volumes in left caudal middle gyrus in the frontal lobe of the WWH sample.

Although these peripheral markers of inflammation were elevated in both the WWH and the whole sample, the more restricted pattern of associated brain volumes in the WWH, along with the result that sCD163 was only significantly correlated with smaller volumes in a region of the frontal lobe in the WWH, suggests a more specific, disease-related mechanism underlying associations. Frontal lobe dysfunction and reduced connectivity has also been described as a common neurological outcome in PWH,[38–40] and our findings are consistent with previous studies showing that PWH tend to have smaller frontal lobe volume and less frontal connectivity.[41,42] Although peripheral inflammation poses a threat to CNS integrity in any individual with a chronic disease, these soluble monocyte markers may be a more salient and specific marker of an HIV-related neuropathology, instead of a general inflammatory process.

Peripheral inflammation is neurotoxic through indirect mechanisms because neurons cannot directly be infected by HIV.[43] Activation of peripheral monocytes and subsequent migration into the CNS compartment has been shown in the acute phase of HIV infection.[44] By compromising neurovasculature,[27,45,46] infecting microglia, increasing the concentrations of chemokines and monocyte-derived proteins,[47,48] and the establishment of a CNS viral reservoir,[49] the local environment of neurons is threatened, increasing the likelihood of neurological dysfunction and cognitive impairments. Furthermore, persistent inflammation can be worsened by lifestyle factors that are more common in PWH, such as chronic exposure to stress and/or trauma.[50–52]

This present analysis accounted for a number of factors that are associated with poorer neurocognitive functioning in both WWH and HIV-seronegative women, such as age, body mass index, and depressive symptoms. However, it is also

worth highlighting that even when the HIV-seronegative women were removed from the analysis altogether, sCD14 remained associated with smaller frontal volumes in several regions in WWH, and sCD163 was also found to be associated with the left caudal middle frontal gyrus. These peripheral markers may potentially be more salient markers of neurocognitive decline particularly among WWH because they are at presumably higher risk for a confluence of age-, HIV-, and sex-related effects of persistent overactivation of inflammatory cascades[53] both peripherally and centrally. In addition, brain volume and inflammatory response biomarkers in these WWH may also each be affected by several other comorbid factors: stress exposure,[54,55] depression symptoms,[56] APOE expression,[57] or simply older age.[58–61] In our sample, however, symptoms of depression and stress exposure were also significantly correlated with each other, and for simplicity of analysis, we included the strongest factor, depressive symptoms, into both models. Still, each of these may further alter or mediate the relationship between these primary outcome variables, although the study design and sample size precluded exploration of these additional research questions.

Finally, although this is the only study of WWH studied to date, the main limitation of this study design was a relatively small sample size, replicating this analysis with a larger subject pool would likely reveal a clearer distinction between how the relationship between inflammatory markers and brain volume differs between the WWH and the control group. The cross-sectional design of this study analysis gives interesting insight into associations between inflammatory biomarkers and brain volumes in WWH, but without a larger sample and further analysis of group differences in the strength of these associations, causation and/or underlying mechanisms cannot yet be determined.

In conclusion, our results demonstrated that, although elevated sCD14 is associated with smaller volumes in individuals with and without HIV, increased concentrations of sCD14 and sCD163 are particularly associated with smaller frontal lobe brain volumes in WWH. Larger scale, longitudinal studies are needed to replicate these findings and to consider potentially characterizing how to control these inflammatory processes or at least attempt to mitigate the neurological effects of HIV-related inflammation, to help ensure optimal neurological function in these women in the years and decades to come.

REFERENCES

1. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity.* 2013;39:633–645.
2. Deeks SG. Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy. *Top HIV Med.* 2009;17:118–123.
3. Klatt NR, Chomont N, Douek DC, et al. Immune activation and HIV persistence: implications for curative approaches to HIV infection. *Immunological Rev.* 2013;254:326–342.
4. Neuhaus J, Jacobs DR Jr, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis.* 2010;201:1788–1795.
5. Burdo TH, Lackner A, Williams KC. Monocyte/macrophages and their role in HIV neuropathogenesis. *Immunological Rev.* 2013;254:102–113.
6. Dheen ST, Kaur C, Ling EA. Microglial activation and its implications in the brain diseases. *Curr Med Chem.* 2007;14:1189–1197.
7. Estes JD, Harris LD, Klatt NR, et al. Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathog.* 2010;6:e1001052.
8. Guaraldi G, Lonardo A, Maia L, et al. Metabolic concerns in aging HIV-infected persons: from serum lipid phenotype to fatty liver. *AIDS.* 2017; 31(suppl 2):S147–S156.
9. Kis O, Sankaran-Walters S, Hoque MT, et al. HIV-1 alters intestinal expression of drug transporters and metabolic enzymes: implications for antiretroviral drug disposition. *Antimicrob Agents Chemother.* 2016;60: 2771–2781.
10. Martin-Iguacel R, Negredo E, Peck R, et al. Hypertension is a key feature of the metabolic syndrome in subjects aging with HIV. *Curr Hypertens Rep.* 2016;18:46.
11. Nemeth CL, Bekhbat M, Neigh GN. Neural effects of inflammation, cardiovascular disease, and HIV: parallel, perpendicular, or progressive? *Neuroscience.* 2015;302:165–173.
12. Kusao I, Shiramizu B, Liang CY, et al. Cognitive performance related to HIV-1-infected monocytes. *J Neuropsychiatry Clin Neurosci.* 2012;24: 71–80.
13. 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.
14. Williams DW, Veenstra M, Gaskill PJ, et al. Monocytes mediate HIV neuropathogenesis: mechanisms that contribute to HIV associated neurocognitive disorders. *Curr HIV Res.* 2014;12:85–96.
15. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med.* 2006;12:1365–1371.
16. Klatt NR, Funderburg NT, Brenchley JM. Microbial translocation, immune activation, and HIV disease. *Trends Microbiol.* 2013;21:6–13.
17. Leeansyah E, Malone DF, Anthony DD, et al. Soluble biomarkers of HIV transmission, disease progression and comorbidities. *Curr Opin HIV AIDS.* 2013;8:117–124.
18. Sandler NG, Wand H, Roque A, et al. Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis.* 2011;203: 780–790.
19. Shive CL, Jiang W, Anthony DD, et al. Soluble CD14 is a nonspecific marker of monocyte activation. *AIDS.* 2015;29:1263–1265.
20. Burdo TH, Lentz MR, Autissier P, et al. Soluble CD163 made by monocyte/macrophages is a novel marker of HIV activity in early and chronic infection prior to and after anti-retroviral therapy. *J Infect Dis.* 2011;204:154–163.
21. Castley A, Berry C, French M, et al. Elevated plasma soluble CD14 and skewed CD16+ monocyte distribution persist despite normalisation of soluble CD163 and CXCL10 by effective HIV therapy: a changing paradigm for routine HIV laboratory monitoring? *PLoS One.* 2014;9: e115226.
22. Steinbrink F, Evers S, Buerke B, et al. Cognitive impairment in HIV infection is associated with MRI and CSF pattern of neurodegeneration. *Eur J Neurol.* 2013;20:420–428.
23. Imp BM, Rubin LH, Tien PC, et al. Monocyte activation is associated with worse cognitive performance in HIV-infected women with virologic suppression. *J Infect Dis.* 2017;215:114–121.
24. Royal W III, Cherner M, Burdo TH, et al. Associations between cognition, gender and monocyte activation among HIV infected individuals in Nigeria. *PLoS One.* 2016;11:e0147182.
25. Kallianpur KJ, Valcour VG, Lerdlum S, et al. HIV DNA in CD14+ reservoirs is associated with regional brain atrophy in patients naive to combination antiretroviral therapy. *AIDS.* 2014;28:1619–1624.
26. 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.
27. Avison MJ, Nath A, Greene-Avison R, et al. Inflammatory changes and breakdown of microvascular integrity in early human immunodeficiency virus dementia. *J Neurovirol.* 2004;10:223–232.
28. Burdo TH, Lo J, Abbara S, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. *J Infect Dis.* 2011;204: 1227–1236.
29. Nottet HS. Interactions between macrophages and brain microvascular endothelial cells: role in pathogenesis of HIV-1 infection and blood-brain barrier function. *J Neurovirol.* 1999;5:659–669.

30. Colon K, Perez-Laspiur J, Quiles R, et al. Macrophage secretome from women with HIV-associated neurocognitive disorders. *Proteomics Clin Appl.* 2016;10:136–143.
31. Martin GE, Gouillou M, Hearps AC, et al. Age-associated changes in monocyte and innate immune activation markers occur more rapidly in HIV infected women. *PLoS One.* 2013;8:e55279.
32. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;24:385–396.
33. Weathers FW, Huska JA, Keane TM. *PCL-C for DSM-IV*. Boston, MA: Division NCfPBS; 1991.
34. Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977;1:385–401.
35. Dewey J, Hana G, Russell T, et al. Reliability and validity of MRI-based automated volumetry software relative to auto-assisted manual measurement of subcortical structures in HIV-infected patients from a multisite study. *Neuroimage.* 2010;51:1334–1344.
36. Labate A, Cerasa A, Aguglia U, et al. Voxel-based morphometry of sporadic epileptic patients with mesiotemporal sclerosis. *Epilepsia.* 2010; 51:506–510.
37. Ances BM, Ortega M, Vaida F, et al. Independent effects of HIV, aging, and HAART on brain volumetric measures. *J Acquir Immune Defic Syndr.* 2012;59:469–477.
38. Hines LJ, Miller EN, Hinkin CH, et al. Cortical brain atrophy and intra-individual variability in neuropsychological test performance in HIV disease. *Brain Imaging Behav.* 2016;10:640–651.
39. Sanford R, Fernandez Cruz AL, Scott SC, et al. Regionally specific brain volumetric and cortical thickness changes in HIV-infected patients in the HAART era. *J Acquir Immune Defic Syndr.* 2017;74:563–570.
40. Towgood KJ, Pitkanen M, Kulasegaram R, et al. Mapping the brain in younger and older asymptomatic HIV-1 men: frontal volume changes in the absence of other cortical or diffusion tensor abnormalities. *Cortex.* 2012;48:230–241.
41. Pfefferbaum A, Rogosa DA, Rosenbloom MJ, et al. Accelerated aging of selective brain structures in human immunodeficiency virus infection: a controlled, longitudinal magnetic resonance imaging study. *Neurobiol Aging.* 2014;35:1755–1768.
42. 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.
43. Gonzalez-Scarano F, Martin-Garcia J. The neuropathogenesis of AIDS. *Nat Rev Immunol.* 2005;5:69–81.
44. 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.
45. Crystal HA, Weedon J, Holman S, et al. Associations of cardiovascular variables and HAART with cognition in middle-aged HIV-infected and uninfected women. *J Neurovirol.* 2011;17:469–476.
46. Cysique LA, Moffat K, Moore DM, et al. HIV, vascular and aging injuries in the brain of clinically stable HIV-infected adults: a (1)H MRS study. *PLoS One.* 2013;8:e61738.
47. Garden GA. Microglia in human immunodeficiency virus-associated neurodegeneration. *Glia.* 2002;40:240–251.
48. Kaul M, Lipton SA. Chemokines and activated macrophages in HIV gp120-induced neuronal apoptosis. *Proc Natl Acad Sci U S A.* 1999;96: 8212–8216.
49. Veenstra M, Leon-Rivera R, Li M, et al. Mechanisms of CNS viral seeding by HIV(+) CD14(+) CD16(+) monocytes: establishment and reseeding of viral reservoirs contributing to HIV-associated neurocognitive disorders. *mBio.* 2017;8:e01280–17.
50. Cruess DG, Leserman J, Petitto JM, et al. Psychosocial-immune relationships in HIV disease. *Semin Clin Neuropsychiatry.* 2001;6: 241–251.
51. Evans DL, Leserman J, Perkins DO, et al. Severe life stress as a predictor of early disease progression in HIV infection. *Am J Psychiatry.* 1997; 154:630–634.
52. Starr KR, Antoni MH, Hurwitz BE, et al. Patterns of immune, neuroendocrine, and cardiovascular stress responses in asymptomatic HIV seropositive and seronegative men. *Int J Behav Med.* 1996;3: 135–162.
53. Krebs SJ, Slike BM, Sithinamsuwan P, et al. Sex differences in soluble markers vary before and after the initiation of antiretroviral therapy in chronically HIV infected individuals. *AIDS.* 2016;30:1533–1542.
54. Hantsoo L, Kornfield S, Iannelli C, et al. Glucocorticoid-immune response to acute stress in women and men living with HIV. *J Behav Med.* 2019;42:1153–1158.
55. Masia M, Padilla S, Fernandez M, et al. Oxidative stress predicts all-cause mortality in HIV-infected patients. *PLoS One.* 2016;11:e0153456.
56. Vance DE, Fazeli PL, Grant JS, et al. The role of neuroplasticity and cognitive reserve in aging with HIV: recommendations for cognitive protection and rehabilitation. *J Neurosci Nurs.* 2013;45:306–316.
57. Chang L, Andres M, Sadino J, et al. Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. *Neuroimage.* 2011;58:1017–1027.
58. Anderson AM, Harezlak J, Bharti A, et al. Plasma and cerebrospinal fluid biomarkers predict cerebral injury in HIV-infected individuals on stable combination antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2015; 69:29–35.
59. Avison MJ, Nath A, Greene-Avison R, et al. Neuroimaging correlates of HIV-associated BBB compromise. *J Neuroimmunol.* 2004;157:140–146.
60. Chang L, Wong V, Nakama H, et al. Greater than age-related changes in brain diffusion of HIV patients after 1 year. *J Neuroimmune Pharmacol.* 2008;3:265–274.
61. Desai S, Landay A. Early immune senescence in HIV disease. *Curr HIV/AIDS Rep.* 2010;7:4–10.