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Variability in C-reactive protein is associated with cognitive impairment in women living with and without HIV: A longitudinal study

Leah H. Rubin[1,2], **Lorie Benning**[3], **Sheila M. Keating**[4], **Philip J. Norris**[4], **Jane Burke-Miller**[5], **Antonia Savarese**[1], **Krithika N. Kumanan**[6], **Saria Awadalla**[6], **Gayle Springer**[3], **Kathyrn Anastos**[7], **Mary Young**[8], **Joel Milam**[9], **Victor G. Valcour**[10], **Kathleen M. Weber**[5], and **Pauline M. Maki**[1,11]

[1]Department of Psychiatry, University of Illinois at Chicago, Chicago, IL

[2]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

[3]Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

[4]Blood Systems Research Institute, San Francisco, CA

[5]Cook County Health and Hospitals System/Hektoen Institute of Medicine, Chicago, IL

[6]School of Public Health, Division of Epidemiology and Biostatistics, University of Illinois at Chicago, Chicago

[7]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY

[8]Department of Medicine, Georgetown University, Washington, DC

[9]Institute for Health Promotion and Disease Prevention Research, Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA

[10]Memory and Aging Center, Department of Neurology, University of California, San Francisco

[11]Department of Psychology, University of Illinois at Chicago, Chicago, IL

Abstract

Despite the availability of effective antiretroviral therapies, cognitive impairment (CI) remains prevalent in HIV-infected (HIV+) individuals. Evidence from primarily cross-sectional studies, in predominantly male samples implicates monocyte and macrophage-driven inflammatory processes linked to HIV-associated CI. Thus, peripheral systemic inflammatory markers may be clinically useful biomarkers in tracking HIV-associated CI. Given sex differences in immune function, we focused here on whether mean and intraindividual variability in inflammatory markers predicted CI in HIV+ and HIV− women. Seventy-two HIV+ (36 with CI) and 58 HIV− (29 with CI) propensity-matched women participating in the Women's Interagency HIV Study completed a

Address correspondence and reprint requests 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, Phone: 443-287-0571, Fax: 410-955-0672, lrubin1@jhmi.edu.

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neuropsychological battery once between 2009–2011 and performance was used to determine CI status. Analysis of 13 peripheral immune markers was conducted on stored biospecimens at 3 time points (7 and 3.5 years before neuropsychological data collection and concurrent with data collection). HIV+ women showed alterations in 8 immune markers compared to HIV− women. The strongest predictors of CI across HIV+ and HIV− women were lower mean soluble tumor necrosis factor receptor I (sTNFRI) levels, higher mean interleukin (IL)-6 levels, and greater variability in C-reactive protein (CRP) and matrix metalloproteinase (MMP)-9 (p's<0.05). Stratified by HIV, the only significant predictor of CI was greater variability in CRP for both HIV + and HIV− women (p's<0.05). This variability predicted lower executive function, attention/working memory, and psychomotor speed in HIV+ but only learning in HIV− women (p's<0.05). Intraindividual variability in CRP levels over time may be a good predictor of CI in predominately minority low socioeconomic status midlife women.

Keywords

HIV; Cognition; Inflammation; Women; CRP

Introduction

HIV-associated cognitive impairment (CI) remains a major clinical issue in HIV care despite combination antiretroviral therapy (cART). Although the incidence of dementia has markedly decreased in the cART era, 30-60% of individuals living with HIV will exhibit CI during their lifetime (Grant, 2008). The pathophysiology of HIV-associated CI in the cART era remains incompletely understood and is a high priority issue in HIV research.

HIV-associated CI may result from direct neurotoxic effect of the virus itself or via the shedding of viral proteins such as Tat and gp120 (D'Aversa *et al*, 2005; Haughey and Mattson, 2002; Li *et al*, 2005). There is also compelling evidence that HIV-associated CI may result from indirect neurotoxic immunological processes mediated by cells of the monocyte/macrophage lineage (Burdo *et al*, 2013a; Hong and Banks, 2015; Kaul *et al*, 2001; Langford and Masliah, 2001; Valcour *et al*, 2010). Activated HIV-infected monocytes traffic across the blood brain barrier, infecting microglia and macrophages which in turn lead to an overexpression of cytokines and chemokines and initiation of an astrocyte-induced inflammatory cascade (Eugenin *et al*, 2011; Kou *et al*, 2009; Vartak-Sharma *et al*, 2014; Wang *et al*, 2008). Even with suppressive cART, HIV-induced inflammation can result in brain injury (Vera *et al*, 2016).

The role of neuroinflammation as a major contributor of brain injury has been examined in studies where peripheral systemic inflammatory markers are used as indicators of neuroinflammation. In neuroimaging studies for example, plasma and CSF inflammatory biomarkers are strongly associated with adverse alterations in brain structure and function (Ances and Hammoud, 2014; Anderson *et al*, 2015a; Anderson *et al*, 2015b; Bora *et al*, 2014). The state of the science is primarily based on largely male-dominant samples and cross-sectional studies. Given substantial evidence of sex differences in neuroimmune activation (Martin *et al*, 2013; Mathad *et al*, 2016; Ticona *et al*, 2015) and cognition (Failde-

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Garrido *et al*, 2008; Heaton *et al*, 2015; Robertson *et al*, 1996; Royal *et al*, 2016), previous findings might not be generalizable to HIV-infected women. Moreover, longitudinal studies are needed to enhance our understanding of the time course of CI in relation to altered immune function, including whether absolute levels and/or variability in these biomarkers over time relate to HIV-associated CI.

In a prospective, nested, case-control study, we examine the time course of inflammatory and immune biomarkers over a 6-year time period and the extent to which those biomarkers predict CI at the 6-year mark. We include four groups of women that differ in HIV serostatus (HIV+ versus HIV−) and CI (present or absent at 6 years). The selected biomarkers have shown differences by HIV-serostatus, associations with cognitive performance in HIV+ individuals, and/or associations with cognitive performance in other individuals (Cohen *et al*, 2011a; Cohen *et al*, 2011b; Correia *et al*, 2013a; Koyama *et al*, 2013; Singh and Newman, 2011). We hypothesized that regardless of HIV status, mean levels and variability in interleukin (IL)-6, IL-10, IL-16, IL-18, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), interferon-gamma inducible protein (IP)-10, monocyte chemoattractant protein (MCP)-1, MCP-9, soluble TNFR(receptor) I&II, and macrophage inflammatory protein (MIP)-1β would be predictors of prevalent CI. However, we expected that mean levels and variability in IL-6, IL-10, TNF-α, CRP would be stronger predictors of prevalent CI among HIV+ women than among HIV- women and that IL-1β and TNF-related apoptosis inducing ligand (TRAIL) would be specific predictors of prevalent CI among HIV+ women.

Methods

Study Sample

Participants were enrolled in the WIHS, an ongoing longitudinal, multi-site cohort study of HIV+ and socio-demographically similar HIV− women (http://wihshealth.org). For this prospective, nested case/control study, we used participants enrolled in the first two waves who also subsequently completed baseline neuropsychological (NP) testing between 2009 and 2011 (for complete information regarding demographics, behavioural, and clinical characteristics see (Maki *et al*, 2015). The first wave of data collection occurred between October 1994 and November 1995 and the second between October 2001 and September 2002 at six sites (Brooklyn, Bronx, Chicago, DC, Los Angeles, and San Francisco). Detailed information regarding recruitment procedures, eligibility criteria, and study methods have been previous published (Bacon *et al*, 2005; Barkan *et al*, 1998).

To determine which cases were selected for analyses (see Supplemental Table 1 for the distribution of CI for HIV+ and HIV− women), we used propensity matching which reduces case-control selection bias (Walsh *et al*, 2012). A single logistic regression model was used to obtain propensity scores where the outcome was case status and predictors were HIV status; age; years of education; Wide Range Achievement Test (WRAT-R) reading subset score; race/ethnicity (African-American, Latina, White, Other), HCV status at baseline (HCV Ab[antibody]-, HCV Ab+ RNA−, HCV Ab+ RNA unknown, HCV Ab+ RNA+); body mass index; current smoker; recent marijuana use; recent crack, cocaine, and/or heroin use; alcohol use (none, light (0-7 drinks/week), moderate (7-12 drinks/week), heavy (>12 drinks/week)); depressive symptoms (Center for Epidemiological Studies Depression Scale

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(CES-D) 16 cutoff); self-reported antidepressant use; liver fibrosis (Aspartate aminotransferase platelet ratio index-APRI); and hepatic fibrosis (FIB-4). The matching was implemented separately by HIV status. Using a tolerance of 0.04, HIV+ cases (CI) were matched to HIV+ controls (no CI) and HIV− cases (CI) were matched to HIV− controls (no CI). The goal of propensity matching was to create 4 groups (HIV+ CI, HIV+ no CI, HIV− CI, HIV− no CI) balanced on all covariates included in the matching model which were factors known to be or potentially associated with CI.

Prior to propensity matching, cases were included/excluded from possible selection based on the following factors. Cases available for study inclusion were: 1) availability of specimens at the visit when NP testing occurred (2009–2011) and at one or two earlier visits (2003–2004 and/or 2006–2007), 2) valid completion of all neuropsychological tests in each of the 7 domains, and 3) English speaking. A total of 341 HIV+ no CI, 104 HIV+ CI, 202 HIV− no CI, and 45 HIV− CI met these criteria. Cases excluded from study inclusion were: 1) seroconverters and other rare phenotypes (ART-naïve HAART initiator, long-term non-progressor (CD4 > 500cells/mm3 for ≥5 years, no ART), elite controller (viral load <80 cp/ml for ≥1.5 years, no ART), registry-confirmed incident cancer), 2) CD4 <200 cells/mm3, 3) self-report of a physician diagnosis of dementia, 4) self-reported CVA/stroke, 5) self-reported use of antipsychotic or Alzheimer's medications, 6) visual or health-related issues that could impact performance on the cognitive test battery, 7) staff note indicating that the participant was under the influence of drugs during testing, and 8) women self-reporting neuropathy or complaints of arthritis or damaged fingers which would invalidate performance on grooved pegboard. After exclusion criteria were applied, we were able to select from 167 HIV+ no CI, 36 HIV+ CI, 149 HIV− no CI, and 30 HIV− CI for propensity matching.

Measures

Multiplex cytokine and chemokine analysis

Serum samples were assayed for 2 or 3 longitudinal time points at approximately 3-year intervals using the standard-sensitivity Milliplex Map kit (Millipore) for IL-10, IL-1β, IL-6, IP-10, MCP-1, MIP-1β, and TNF-α, standard-sensitivity Panel II kit (Millipore) for IL-16 and TRAIL, Soluble Receptors kit (Millipore) for soluble TNF receptor type I (sTNFRI) and II (sTNFRII), Matrix Metalloproteinase panel Luminex (Millipore) for MMP-9, R&D Quantikine ELISA for CRP, and MBL international ELISA for IL-18. Standards and samples were tested in duplicate. Beads were acquired on a Labscan analyzer (Luminex) using Bio-Plex manager 6.1 software (Bio-Rad). ELISA was read on a Molecular Devices Emax plate reader and acquired on Softmax Pro (version 5.4). High CV% between repeat samples were flagged and repeated for analyses (Keating *et al*, 2011). To avoid confounding of batch with time and group, all longitudinal samples were run on the same plate, with an equal proportion of the four groups (ratio 2:1 HIV+ to HIV−). The same two controls were run on every plate to evaluate the reliability of values across plates. Values that were determined to be out of range low were assigned 0.5, the lowest standard. The proportion of undetectable values for cytokines was: IL-1β (56%), IL-6 (45%), IL-10 (20%), IL-16 (9%), CRP (2%), MIP-1β (1%), and TRAIL (1%). Values that were extrapolated beyond the

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standard curve were accepted as that value. All immune markers were log transformed and winsorized (<1% of values changed to be equal to the highest or lowest value that was within 3SD of the interquartile range) to normalize distributions.

Primary Outcome

CI status, the primary outcome variable, was based on a neuropsychological test battery completed once between 2009 and 2011. The battery included 8 tests: Hopkins Verbal Learning Test-Revised (HVLT-R), Letter-Number Sequencing, Trail Making (TMT) Stroop Test, Symbol Digit Modalities Test (SDMT), Controlled Oral Word Association Test (COWAT), Category Fluency Test (Animals), and Grooved Pegboard (GPEG). Seven domains were assessed using these tests: **learning** (outcome=total learning across HVLR-T trials), **memory** (outcome=delayed free recall on HVLT-R), **attention/working memory** (outcomes=total correct on LNS control and experimental conditions), **psychomotor speed** (outcomes=total correct on SDMT, time to completion on Stroop Trial 2), **executive function** (outcomes =time to completion on TMT Part B and Stroop Trial 3), **fluency** (outcomes=total correct on COWAT and category fluency), and **motor skills** (outcomes=total time to completion for each hand on GPEG). Timed outcomes were log transformed to normalize distributions and reverse scored so higher values equated to better performance.

Consistent with previous large-scale HIV cohorts (Cysique *et al*, 2014; Heaton *et al*, 2004; Sacktor *et al*, 2016) including WIHS (Maki *et al*, 2015; Rubin *et al*, 2015; Rubin *et al*, 2016), demographically adjusted T-scores were derived for each outcome and these T-scores were used to create domain scores (Supplemental Materials). CI was defined as scoring below the expected level of performance (T-score <40) in at least 3 of 7 domains. Although only two domains of CI are typically required for a diagnosis of HIV-Associated Neurocognitive Disorder (HAND) (Antinori *et al*, 2007), we chose a more stringent definition because at the time we did not have measures necessary to determine HAND, including instrumental activities of daily living.

Statistical analysis

A series of conditional logistic regression models were conducted in SAS (version 9.4, Cary, NC) to assess whether average or fluctuation (standard deviation) in inflammatory biomarkers over all time points tested predicted CI in general (using overall sample) or whether they differentially predicted HIV-associated CI (stratified by HIV-serostatus). Conditional logistic regression models were selected to handle the nested propensity-matched pair design (65 pairs). Unadjusted models were first conducted to examine the association of primary predictor variables to CI. Primary predictor variables were average levels and variability (standard deviation) of the 13 inflammatory markers from all time points. Based on these models, all predictors associated with the outcome at $p<0.10$ were included in a stepwise model. The study design prohibited the inclusion of HIV status in models for the overall sample; the proportion of cases was exactly 50% in both HIV+ and HIV− women. Variables were retained in the stepwise models if $p<0.10$. Odds ratios (ORs) and 95% CIs were calculated using maximum likelihood estimates from the conditional logistic regression models. When inflammatory markers were predictive of CI among HIV+

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women, models were rerun including HIV-specific covariates (viral load, current and nadir CD4 count, and CD4/CD8 ratio). Additionally, when inflammatory markers were predictive of CI in either group, exploratory correlational analyses using Spearman's Rho were conducted to determine the specific domains contributing to the global effect. Because exploratory analyses were performed for heuristic purposes to examine the potential clinical significance for future larger scale studies, we did not correct for multiple comparisons. However, given the small sample sizes, when correlations were observed ($p<0.10$), bootstrapping of the correlation coefficient (based on 1000 samples) was conducted to determine the strength of the associations and to ensure findings were not driven by outliers. The 95%CI from the bootstrapping procedure was used to determine statistical significance (95%CI does not include 0).

Results

Sample Characteristics

The overall sample of 130 women was 67% African-American, non-Hispanic and 20% Hispanic and ranged in age from 25-70 years (mean=43.9, SD=9.6) which is comparable to previously published large-scale WIHS studies (Maki *et al*, 2015; Rubin *et al*, 2016). The four groups were comparable across a range of sociodemographic, behavioral, and clinical characteristics (Table 1). Among those with CI, there was a similar prevalence of CI across all domains except psychomotor speed which was more prevalent among HIV+ compared to HIV− women ($p=0.03$, Supplemental Table 2)

Serum Immune biomarkers

Table 2 provides the average of each individual's mean and intra-individual variability (SD) from the two (27 women contributed 54 observations) or three (103 women contributed 309 observations) time points of immune marker levels as a function of HIV status. There were no significant differences in immune marker levels (mean or SD) as a function of having two or three time points. Compared to HIV− women, HIV+ women showed higher mean levels of IL-18, sTNFRII, MCP-1, IP-10, TNF-α, and TRAIL and lower mean levels of IL1-β and IL-6 (p's<0.05). After controlling the false discovery rate (FDR) using the Benjamini-Hochberg procedure only two markers did not remain significant: TRAIL and IL1-β. HIV+ women also showed greater individual variability in sTNFRII and TRAIL compared HIV− women ($p<0.05$); however, these differences did not remain after controlling the FDR. Similar results were seen when comparing women with HIV RNA<80cp/ml and HIV− women. Of the markers showing HIV-serostatus differences, higher viral load was associated with lower mean levels of TRAIL ($r_s=-0.28$, $p=0.02$) and sTNFRII ($r_s=-0.24$, $p=0.04$). Lower CD4/CD8 ratio was associated with higher mean levels of TNF-α ($r_s=-0.42$, $p<0.0001$), IL1-β ($r_s=-0.32$, $p=0.007$), IL-6 ($r_s=-0.32$, $p=0.007$), and TRAIL ($r_s=-0.27$, $p=0.03$). These markers were not significantly associated with current or nadir CD4 count (p's>0.07).

Table 3 provides the results from the unadjusted conditional logistic regression models across HIV+ and HIV− groups to assess general predictors of CI as well as stratified by serostatus to assess for specific predictors of HIV-associated CI. In unadjusted analyses, the

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strongest predictors of CI in the overall sample were lower mean levels of sTNFRI (p=0.009) and greater variability in CRP (p=0.003), with trends for higher mean levels of IL-6 (p=0.08) and greater variability in MMP-9 (p=0.08). In adjusted analyses, all four of these biomarkers were significant predictors of CI: mean levels of sTNFRI (OR 0.07 95%CI 0.01-0.46, p=0.006), mean levels of IL-6 (OR 1.54, 95%CI 1.09-2.18, p=0.01), variability in CRP (OR 4.66, 95%CI 1.52-14.24, p=0.007), and variability in MMP-9 (OR 16.85, 95%CI 1.98-143, p=0.009). In unadjusted analyses in HIV+ women only, the only significant predictor of CI was increased variability in CRP levels (p=0.04). CRP remained significant (p=0.04) after adjusting for viral load, CD4 count (current and nadir), and the CD4/CD8 ratio (p's NS). In unadjusted analyses in HIV− women, the strongest predictors of CI were lower mean levels of sTNFRI (p=0.04) and increased variability in CRP (p=0.03), but only increased variability in CRP remained significant in adjusted analyses (OR 4.21, 95%CI 1.14-15.49).

Follow-up exploratory analyses in the overall sample indicated that lower mean level of sTNFRI was associated with lower performance in psychomotor speed (r_S=0.18, p=0.04, 95%CI 0.01 to 0.35), attention/working memory (r_S=0.25, p=0.005, 95%CI 0.10-0.41), and fluency (r_S=0.28 p=0.001, 95%CI 0.11 to 0.44). Greater variability in MMP-9 levels were associated with lower performance on fluency (r_S=−0.18, p=0.04, 95%CI −0.37 to −0.01) whereas greater variability in CRP levels was associated with worse executive function (95%CI −0.41 to −0.07), psychomotor speed (95%CI −0.38 to −0.07), attention/working memory (95%CI −0.37 to −0.04), and learning (95%CI −0.36 to −0.04) (Fig 1). Greater variability in CRP levels was the strongest correlate of psychomotor speed, attention/working memory, and executive function in HIV+ (p's<0.05; 95%CI <−0.01) and learning in HIV− women (p=0.04, 95%CI −0.51 to −0.02)(Fig 1). Similar results were seen among HIV + women after adjusting for viral load and CD4 count (current and nadir) (p's NS).

Discussion

Extending previous cross-sectional studies in predominantly male samples, we conducted a prospective, nested case-control study to determine if peripheral inflammatory markers over time predict CI in HIV+ women and HIV– women. Our conclusions support the finding of consistent immune alterations despite ART. Consistent with previous studies, serum levels of cytokines (IL-6, IL-18, TNF-α, IL-1β) and their receptors (sTNFRII, TRAIL) as well as chemokines (MCP-1, IP- 10) differed between a sample of predominately cART treated (96%) and virologically supressed (93%) HIV+ women and HIV− women (Cohen *et al*, 2011a; Correia *et al*, 2013b; Deeks *et al*, 2013; Neuhaus *et al*, 2010; Ronsholt *et al*, 2013). Importantly, there was no bias in which group contributed two or three samples. We found more robust HIV-serostatus differences when examining mean levels of immune markers but also found differences when examining intra-individual variability in immune markers (sTNFRII, TRAIL; CRP and IL-18 trends) a metric that can only be examined with multiple measurements.

Although most studies report HIV-serostatus differences in immune markers, the patterns and markers themselves are not always consistent across studies. Compared to HIV− women, HIV+ women in the present study showed lower levels of IL-6 and IL-1β and

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higher levels of IL-18, TNF-α, sTNFRII, TRAIL, MCP-1, and IP-10. These findings are partially consistent with previous studies (Cohen *et al*, 2011a; Correia *et al*, 2013b; Neuhaus *et al*, 2010; Ronsholt *et al*, 2013). For example, Neuhaus *et al*. (2010) found that ART-treated men and women had approximately 40 to 60% higher IL-6 levels compared to controls. Others have reported lower levels of TNF-α in HIV+ compared to HIV− individuals, no differences in TRAIL, and elevated levels of MIP-1β (Cohen *et al*, 2011a; Correia *et al*, 2013b). Inconsistencies across studies could be due to a numerous factors such as the examination of mixed samples of men and women, using a single measurement versus our use of average levels across multiple time points, or the inclusion of individuals co-infected with HCV. This study includes individuals co-infected with HCV, albeit a similar proportion across the 4 groups.

Our findings also provide support for the role of inflammation in CI in HIV− individuals. In the overall sample, IL-6, CRP, sTNFRI, and MMP-9 predicted CI. Among population studies of aging, IL-6, CRP, and TNF-α are among the most studied markers of adverse outcomes including cognitive decline (see Singh and Newman, 2011, for review). Many, but not all studies, demonstrate associations between these general markers of systemic low-grade inflammation and cognitive performance and/or decline as well as all-cause dementia. For example, findings from the Northern Manhattan Study, a large community-based prospective cohort of older HIV-uninfected socioeconomically and ethnically diverse sample of men and women, demonstrated that elevated IL-6 levels were associated with lower cognitive performance (Wright *et al*, 2006) and greater cognitive decline (Economos *et al*, 2013).

Our strongest effects of predictors of prevalent CI were with variability in CRP levels. While Economos *et al*. (2013) did not demonstrate an association between CRP and cognitive decline, others have demonstrated this association with absolute levels of CRP (Noble *et al*, 2010; Puzianowska-Kuznicka *et al*, 2016; Roberts *et al*, 2009; Yaffe *et al*, 2003) and with variability in CRP levels (Metti *et al*, 2014). In a meta-analysis, CRP was associated with a 45% increase in all-cause dementia and IL-6 was associated with a 32% increase (Koyama *et al*, 2013). Variability in CRP has been observed in other settings (Bogaty *et al*, 2013) and might be related to the presence of and variability in inflammation and immune status, weight gain, physical activity, vascular and metabolic conditions, and/or psychological symptoms (Metti *et al*, 2014) as CRP is associated with each of these comorbidities (DeGoma *et al*, 2012; Koenig *et al*, 2003; Ladwig *et al*, 2005; Puzianowska-Kuznicka *et al*, 2016). Larger longitudinal studies with more frequent measurements are needed to identify any particularly meaningful pattern in variability in CRP and any mediators (e.g., vascular) of these associations. As with other biomarkers shown to predict HIV-related CI (e.g., neuroimaging biomarkers), CRP may have limited clinical utility. Rather, the value of these findings is in identifying the mechanisms contributing to HIV− associated CI so that they can be targeted through appropriate interventions.

Greater variability in MMP-9 levels was also a significant predictor of CI in the overall sample. MMP-9, a major secretion product of macrophages, is implicated in the breakdown and remodelling of the extracellular matrix in normal and pathological inflammatory processes (Klein and Bischoff, 2011). HIV can both downregulate and upregulate MMP-9

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production (Ciborowski *et al*, 2004; Muratori *et al*, 2007). Neurotoxic viral proteins gp120 and Tat increase expression of MMP-9 and consequently induce blood brain barrier permeability by degrading vascular tight junction proteins in endothelial cells (Louboutin *et al*, 2010; Xu *et al*, 2012). Thus, MMP-9-related disruption of the blood brain barrier may play a critical role in CI generally and in the pathogenesis of HAND (Avison *et al*, 2004).

In stratified analyses only variability in CRP levels remained a significant predictor of CI in HIV+ and HIV- women. In exploratory analyses in HIV+ women, greater variability in CRP was associated with lower performance on a broad range of cognitive abilities including psychomotor speed, attention/working memory, and executive function. Conversely, in HIV − women, greater CRP variability was associated only with lower learning. CRP may influence cognitive performance differently in HIV+ compared with HIV− individuals. The robustness of these differences and the mechanisms leading to different patterns warrant further investigation.

Limitations of the present study include the relatively small sample size and unknown cognitive status of participants before 2009. Most likely we are examining prevalent and not incident cases of CI. No peripheral monocyte-driven immune activation markers such as soluble CD163 and CD14 were studied but have shown associations with CI (Burdo *et al*, 2013b; Royal *et al*, 2016) including in the WIHS (Imp *et al*, 2017). While the use of propensity matching yielded four groups that were balanced on a number of sociodemographic, clinical, and behavioural characteristics know to be associated with cognitive impairment, this approach controls only for measured confounders and unmeasured factors can still bias results. Finally, the standard sensitivity assay measured most of the analytes required for this analysis but can cause loss of values at the lower end of detection; however, this did not greatly impact the significant markers found in this study to predict prevalent CI. Sensitivity was more of an issue for IL-1β, IL-6, IL-10, and IL-16 in the present study. A deeper investigation impact of low levels of these cytokines on CI will need to be conducted using more sensitive assays.

In sum, our longitudinal findings in women provide further support for the adverse role of persistent residual immune activation despite cART in HIV+ individuals. Alterations in immune processes predicted CI among both HIV+ and HIV− women. Although variability in CRP, a more general marker of low-grade systemic inflammation, was the strongest predictor in both HIV+ and HIV− women, the specific cognitive correlates of CRP differed across the groups with much broader associations in HIV+ women. Findings warrant further study into possible peripheral immune signatures examined over a longer duration that may differentially predict the patterns of CI over time generally and in HIV+ individuals specifically.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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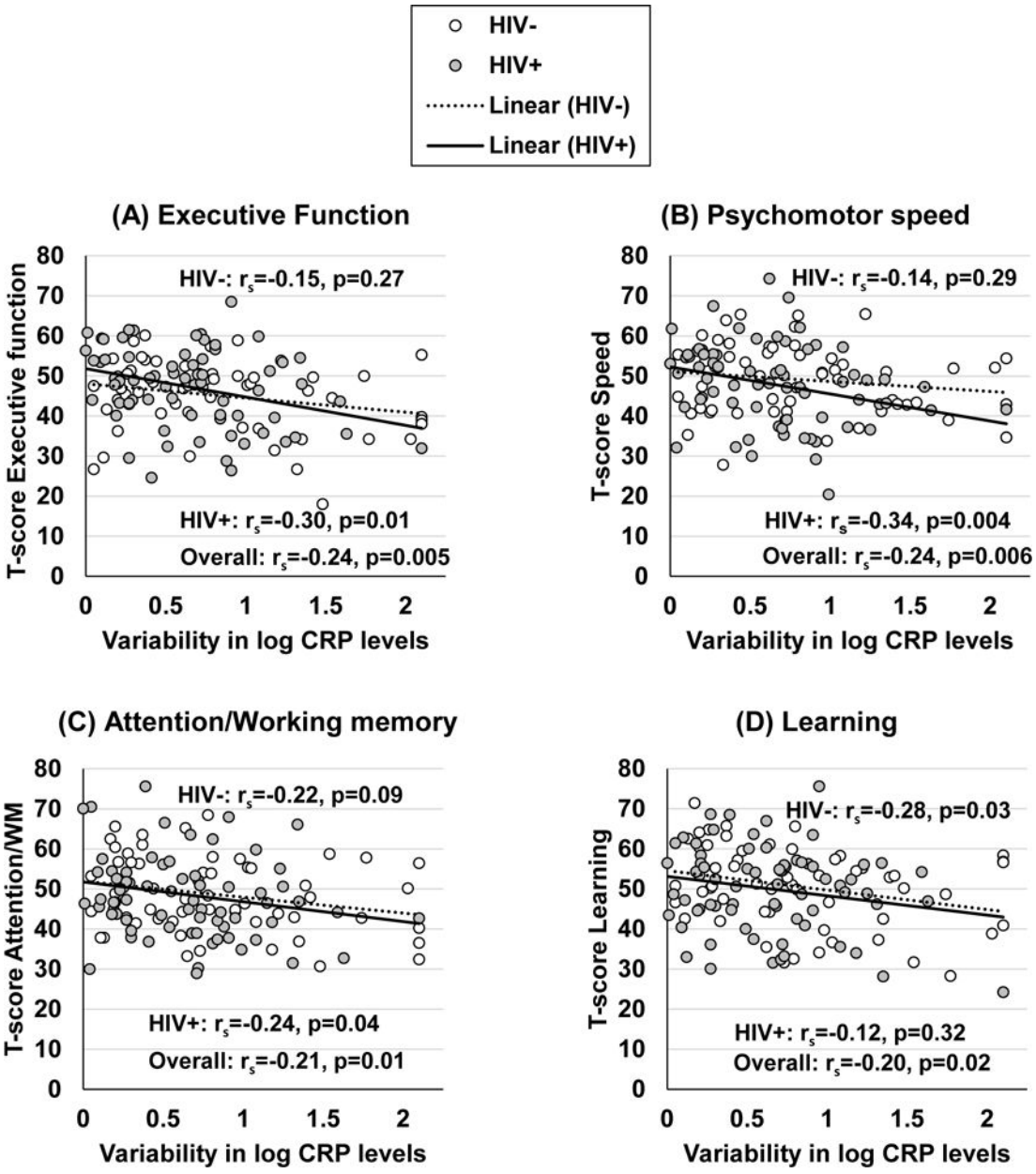

Figure 1.

Mean Variability in log CRP levels predict cognitive performance.

Note. WM=working memory. Mean variability in log CRP levels predicted performance on all of these domains in the overall sample (p's<0.05). CRP is the strongest predictor of attention/working memory, executive function, and psychomotor speed for HIV+ women whereas for HIV- women CRP is the strongest predictor of learning.

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Table 1

Characteristics as a function of cognitive impairment (CI) and HIV-serostatus at the visit concurrent with cognitive data in 2009–2011.

Characteristics	HIV+ CI (n=36)	HIV+ unimpaired (n=36)	HIV− CI (n=29)	HIV− unimpaired (n=29)	p-value
Age, Median (IQR)	46.2 (36.9–51.3)	47.9 (41.2–51.1)	38.9 (33.2–49.4)	43.8 (33.1–51.5)	0.14
Years of education, Median (IQR)	12 (11–12)	12 (11–12)	12 (11–12)	12 (11–12)	0.26
WRAT, Median (IQR)	89 (75–109)	92 (83–101)	90 (84–107)	89 (77–99)	0.91
BMI, Median (IQR)	27.8 (22.6–31.6)	28.3 (23.9–32.7)	27.7 (23.4–36.7)	30.7 (24.1–37.4)	0.49
Apri, Median (IQR)	0.24 (0.15–0.39)	0.26 (0.17–0.39)	0.20 (0.15–0.37)	0.20 (0.15–0.35)	0.47
Fib4, Median (IQR)	0.83 (0.59–1.20)	0.89 (0.66–1.23)	0.69 (0.54–1.27)	0.68 (0.48–0.94)	0.33
HCV viremic, n (%)	6 (17)	8 (22)	6 (21)	5 (17)	0.94
Current smoker, n (%)	17 (47)	21 (58)	15 (52)	19 (66)	0.48
Recent marijuana use, n (%)	6 (17)	9 (25)	7 (24)	6 (21)	0.84
Recent crack, cocaine, and/or heroin use, n (%)	0 (0)	1 (3)	3 (10)	2 (7)	0.17
Drinks per week, n (%)					0.91
None to 7	32 (89)	31 (86)	25 (86)	24 (83)	
≥8	4 (11)	5 (14)	4 (14)	5 (17)	
Race, n (%)					0.10
African-American	26 (72)	24 (67)	17 (59)	20 (69)	
Latina	5 (14)	5 (14)	7 (24)	9 (31)	
White/other	5 (14)	7 (19)	5 (17)	0 (0)	
Recent antidepressant use, n (%)	8 (22)	12 (33)	3 (10)	3 (10)	0.07
CES-D >16, n (%)	7 (19)	9 (25)	9 (31)	7 (24)	0.78
Propensity Score, Median (IQR)	0.23 (0.16–0.29)	0.23 (0.16–0.29)	0.20 (0.14–0.26)	0.20 (0.14–0.27)	0.39
Number of visits with specimens, n (%)					0.36
2	9 (25)	7 (29)	8 (28)	3 (10)	
3	27 (75)	29 (81)	21 (72)	26 (90)	
Years between visits with specimens, Median (IQR)					
Visit 1 to Visit 2	2 (2–3)	3 (2–3)	2 (2–3)	3 (2–3)	0.72
Visit 2 to Visit concurrent with cognitive data	3 (2–3)	3 (2–3)	3 (2–3)	3 (2–3)	0.73
HIV-specific characteristics *					
On HAART at visit, n (%)	36 (100)	33 (91)	–	–	0.24

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Characteristics	HIV+ CI (n=36)	HIV+ unimpaired (n=36)	HIV− CI (n=29)	HIV− unimpaired (n=29)	p-value
CD4 cell count, Median (IQR)	641 (379–799)	620 (396–788)	–	–	0.99
CD4 nadir, Median (IQR)	261 (242)	199 (176)			0.64
CD4/CD8 ratio, Median (IQR)	0.77 (0.76)	0.75 (0.46)			0.67
HIV RNA≤80 (undetectable), n (%)	31 (86)	26 (72)	–	–	0.25
Log_{10} HIV RNA among detectables, Median (IQR)	2.3 (2.2–3.1)	2.2 (2.1–3.1)	–	–	0.81

Note: WRAT =Wide Range Achievement Test, scaled score; CES-D=Center for Epidemiologic Studies Depression Scale; HCV = Hepatitis C Virus; Recent use= Use in the past six months; Apri = liver fibrosis; Fib-4 =non-invasive index of hepatic fibrosis. IQR=interquartile range.

*not included in matching model. The four groups were compared using Wilcoxon Mann-Whitney U test on continuous outcomes and Fisher's exact tests for categorical outcomes.

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Table 2

Comparison of mean levels and variability in levels of immune markers over time for HIV+ and HIV− women.

Log levels	HIV+ M (SE)	HIV− M (SE)	p-value
Mean			
IL1-β	−1.6 (0.15)	−1.1 (0.22)	**0.04**
IL-18	5.4 (0.06)	4.8 (0.08)	**<0.001**†
sTNFRII	8.6 (0.03)	8.4 (0.04)	**0.006**†
sTNFRI	7.1 (0.04)	7.1 (0.04)	0.31
MCP-1	4.9 (0.05)	4.7 (0.05)	**0.008**†
IP-10	5.8 (0.09)	5.3 (0.09)	**<0.001**†
TNF-α	1.7 (0.05)	1.6 (0.06)	**0.01**†
TRAIL	3.3 (0.05)	3.1 (0.06)	**0.03**
MIP-1β	3.3 (0.04)	3.4 (0.05)	0.23
IL-6	−1.4 (0.14)	−0.8 (0.20)	**0.01**†
IL-16	2.7 (0.08)	2.8 (0.09)	0.37
IL-10	−0.1 (0.15)	−0.3 (0.20)	0.44
MMP-9	9.7 (0.06)	9.8 (0.07)	0.53
CRP	7.2 (0.16)	7.3 (0.17)	0.51
Standard deviation			
IL1-β	0.9 (0.08)	0.8 (0.12)	0.87
IL-18	0.3 (0.02)	0.2 (0.02)	***0.05***
sTNFRII	0.2 (0.01)	0.1 (0.01)	**0.004**†
sTNFRI	0.1 (0.01)	0.1 (0.01)	0.44
MCP-1	0.2 (0.02)	0.3 (0.02)	0.41
IP-10	0.4 (0.03)	0.4 (0.04)	0.24
TNF-α	0.3 (0.03)	0.3 (0.03)	0.44
TRAIL	0.3 (0.02)	0.2 (0.02)	**0.04**
MIP-1β	0.3 (0.02)	0.3 (0.02)	0.38
IL-6	0.9 (0.10)	0.9 (0.10)	0.94
IL-16	0.4 (0.03)	0.3 (0.03)	0.15
IL-10	0.9 (0.08)	1.0 (0.10)	0.62
MMP-9	0.4 (0.03)	0.4 (0.03)	0.99
CRP	0.6 (0.05)	0.8 (0.08)	***0.07***

Note. Bold are significant based on independent t-tests; bold and italic are trends at p<0.10.

†denotes significance after controlling the false discovery rate (FDR) using the Benjamini-Hochberg procedure. The FDR was set at 10%.

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Table 3

Associations between average and standard deviation of immune marker predicting cognitive impairment among HIV+ and HIV− women separately as well as in the overall sample.

	HIV+	HIV−	Overall
Log levels	**Impairment (vs. none) OR (95%CI)**	**Impairment(vs. none) OR (95%CI)**	**Impairment(vs. none) OR (95%CI)**
Mean			
IL1-β	0.99 (0.68–1.45)	1.03 (0.78–1.36)	1.02 (0.81–1.27)
IL-18	1.51 (0.60–3.77)	1.30 (0.52–3.24)	1.40 (0.73–2.67)
sTNFRII	1.18 (0.24–5.93)	0.58 (0.09–3.66)	0.87 (0.26–2.90)
sTNFRI	0.24 (0.04–1.39)	**0.10 (0.01–0.95)** *	**0.16 (0.04–0.64)** **
MCP-1	1.55 (0.42–5.64)	0.92 (0.27–3.16)	1.18 (0.49–2.87)
IP-10	1.40 (0.75–2.63)	1.16 (0.54–2.50)	1.30 (0.80–2.11)
TNF-α	1.36 (0.50–3.69)	0.87 (0.32–2.36)	1.09 (0.54–2.19)
TRAIL	1.62 (0.46–5.69)	1.69 (0.42–6.84)	1.65 (0.65–4.20)
MIP-1β	2.78 (0.67–11.24)	1.46 (0.40–5.38)	1.99 (0.77–5.19)
IL-6	1.31 (0.89–1.93)	1.19 (0.87–1.65)	***1.24 (0.97–1.59)*** †
IL-16	0.72 (0.36–1.44)	0.67 (0.29–1.54)	0.70 (0.41–1.19)
IL-10	1.12 (0.76–1.65)	1.13 (0.80–1.59)	1.13 (0.87–1.45)
MMP-9	0.58 (0.20–1.67)	0.74 (0.27–1.98)	0.66 (0.32–1.36)
CRP	1.02 (0.71–1.47)	0.70 (0.43–1.16)	0.89 (0.67–1.19)
Standard deviation			
IL1-β	1.13 (0.75–1.71)	1.24 (0.67–2.29)	1.16 (0.83–1.64)
IL-18	1.38 (0.15–12.72)	0.67 (0.02–28.69)	1.15 (0.17–7.71)
sTNFRII	0.63 (0.01–29.74)	2.70 (0.01–704)	1.01 (0.04–23.77)
sTNFRI	42.84 (0.26–999)	0.26 (0.00–39.96)	3.53 (0.11–108.14)
MCP-1	1.43 (0.07–28.73)	0.92 (0.27–3.16)	5.91 (0.55–63.33)
IP-10	0.91 (0.20–4.18)	2.26 (0.21–24.27)	1.20 (0.34–4.27)
TNF-α	3.03 (0.39–23.69)	1.18 (0.12–11.91)	2.02 (0.44–9.26)
TRAIL	0.41 (0.05–3.16)	0.58 (0.03–11.44)	0.45 (0.09–2.45)
MIP-1β	1.32 (0.14–12.67)	8.60 (0.32–228)	2.52 (0.40–15.83)
IL-6	1.09 (0.68–1.73)	1.03 (0.55–1.92)	1.07 (0.73–1.55)
IL-16	1.09 (0.23–5.18)	7.24 (0.42–124.86)	1.78 (0.46–6.85)
IL-10	0.88 (0.50–1.53)	1.24 (0.62–2.49)	1.00 (0.65–1.55)
MMP-9	2.11 (0.28–15.64)	6.37 (0.71–57.11)	***3.59 (0.83–15.62)*** †
CRP	**3.78 (1.09–13.17)** *	**4.21 (1.14–15.49)** *	**3.99 (1.62–9.79)** **

Note.

** p<0.01.

* p<0.05.

† p=0.06.

^{T}p=0.08. bold is significant at p<0.05; bold and italic is a trend at p<0.09.

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