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Plasma cytokine concentrations associated with HIV/Hepatitis C coinfection are related to attention, executive and psychomotor functioning

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Abstract

Cytokine disturbances have been linked to brain dysfunction among HIV-infected people. Past studies have not simultaneously examined a large set of cytokine measures and their relationships to HIV-associated neurocognitive deficits. We hypothesized that performance on measures of attention, and executive and psychomotor functions would be associated with plasma cytokine concentrations in HIV-infected individuals. Plasma samples drawn from 30 HIV-infected and 37 HIV seronegative individuals were analyzed via xMAP multiplexed bead array immunoassay to determine concentrations of thirteen cytokines. Performance on Trail Making A/B, Stroop Test, Letter Number Sequencing, Digit Symbol Coding, Symbol Search, and Grooved Pegboard tests was assessed. Statistical analyses were performed to examine group differences in cytokine concentrations, and associations between cytokine and HIV clinical variables and neurocognitive performance. Significant HIV effects were found on seven of the thirteen cytokines, primarily with respect to interleukins. HIV clinical factors (CD4 and HIV RNA levels, duration of illness, antiretroviral treatment) and hepatitis C status were associated with specific plasma cytokine concentrations. Neurocognitive measures were associated with cytokine concentrations, most consistently among the interleukins and IP-10. Generally, cytokine concentrations were among the strongest predictors of neurocognitive function relative to other clinical factors, which reinforces their potential importance in examining the neuropathological processes of HIV. The findings also point to the potential value of simultaneously examining a panel of biomarkers. The current results suggest that a complex relationship likely exists among cytokines [how?], and that these relationships are mediated not only by HIV infection, but also by antiretroviral treatment and other comorbid conditions.

INTRODUCTION

HIV-associated neurocognitive and behavioral disturbances are well recognized, and continue to occur despite widespread use of highly active antiretroviral therapies (HAART),

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which can very effectively reduce HIV RNA level and enhances the host immune status. HIV crosses the blood brain barrier and enters the brain very soon after initial infection and replicates in perivascular macrophages and microglia1. In this regard, HIV infection triggers inflammatory responses associated with microglial cell activation and attendant release of neurotoxic pro-inflammatory cytokines 2-4. The inflammatory component of HIV infection in the central nervous system (CNS) is regarded as a critical component of HIV-associated brain dysfunction 5-10, with its severity strongly correlating with the abundance of activated monocytes in the brain 11. HIV-associated neuronal loss and dysfunction are mediated by increased apoptosis and axonal degeneration throughout the brain 12-14. Frontal-striatal areas have been implicated 15-21, consistent with findings of attention-executive and psychomotor impairments common in HIV-infected persons. Neuroimaging approaches, such as magnetic resonance spectroscopy (MRS), can detect abnormalities that reflect cerebral inflammation in HIV infected people 22-24. Previous MRS studies in HIV have shown abnormal cerebral metabolites preferentially in the basal ganglia and frontal brain regions. Moreover, specific metabolite levels were demonstrated to be altered in relation to cognitive impairment and brain atrophy 23-26.

Cytokines, especially those with chemotactic properties (chemokines) are thought to play important roles in HIV-related neuronal injury and protection 5-8, 19, 27-37. Increased levels of chemokine gene expression are detectable in brains with HIV encephalitis, and altered levels of various chemokines and cytokines can be measured in the CSF of patients with HIV-associated dementia 11, 29, 38-44. Serum or plasma cytokine levels have been found to be either increased or decreased in HIV-infected individuals, depending on the specific cytokine and on disease status, such as bodily wasting associated with AIDS45-47. In one study, elevated levels of various plasma cytokines were correlated with cognitive impairment in HIV47. Correspondingly, elevated plasma cytokine concentrations have been linked to cognitive impairment in other diseases, including multiple sclerosis and Alzheimer's Disease/mild cognitive impairment 48-60, in which inflammation is thought to exacerbate the underlying disease process. While the bases for cytokines effects on cognition are not well understood, plasma cytokines could be used as peripheral indices of CNS pathology, in concert with neuroimaging and neurocognitive testing, and therefore are of interest as potential biomarkers for assessing HIV-associated brain dysfunction.

Accordingly, we were interested in better understanding the relationship between plasma cytokine levels and cognitive function in HIV. In the present study, we measured plasma cytokines and chemokines in 30 HIV-infected and 34 seronegative individuals enrolled in a prospective study of HIV-associated brain dysfunction. Statistical analyses were performed to identify the plasma markers that were most strongly associated with neurocognitive function, after accounting for HIV clinical factors (e.g., nadir CD4, duration of infection). Given the preponderance of past findings of cognitive deficits in attention/executive functioning and processing speed in HIV-infected individuals 61, 62, we hypothesized that performance in these cognitive domains would be associated with broad-ranging abnormalities of plasma cytokine activation.

METHODS

Clinical Sample

All subjects were enrolled in a Brown University Center for AIDS Research study to examine the effects of HIV on brain function. Informed consent was obtained from all participants. All subjects underwent a clinical evaluation which included a detailed medical history and assessment of HIV disease. Potential participants were excluded if they had evidence of other neurological brain disease (e.g. Alzheimer's disease), traumatic brain injury with loss of consciousness of greater than 10 minutes, prior opportunistic brain

infection secondary to HIV, severe psychiatric illness (i.e., schizophrenia, bipolar illness), or active substance abuse or dependency.

Participants consisted of 64 adults including 37 men and 27 women, 30 of whom were HIV-infected (HIV+), while 34 were HIV-seronegative (HIV−). HIV serostatus was documented by ELISA and confirmed by Western blot test. Twenty-one HIV+ patients, and two HIV− controls were co-infected with hepatitis C (HCV), defined as detectable HCV RNA by PCR. Viral load (HIV RNA by PCR) was classified as detectable or undetectable based on a lower limit of detection of 75 copies/ml. The majority (69.0%) of HIV+ subjects had undetectable viral loads, and most (80.0%) were on stable HAART. Duration of HIV infection ranged from 2 to 26 years. Despite previous immunocompromise as indicated by an average nadir CD4 of 168.6 cells/μl, most (64.3%) HIV-infected subjects had current CD4 counts above 350 cells/μl, indicating reconstituted immune function.

Neurocognitive Measures

All participants were assessed on seven measures of attention-executive functioning and psychomotor processing speed: the Trail Making Test A and B[63], Stroop Test[64], Grooved Pegboard [65, 66], and three subtests from the Wechsler Adult Intelligence Scale-III, including Digit Symbol Coding, Letter Number Sequencing, Symbol Search[67]. The specific cognitive functions assessed by each test are presented in Table 1. These measures were selected based on their sensitivity to HIV-associated neurocognitive impairments in past studies [61, 62, 66, 68-70], and on recommendations of the NIMH workgroup and the World Health Organization on neurobehavioral assessment of HIV [71], and have been used in a number of our previous studies. All have extensive norms, with strong reliability and validity [72-74]. Individual test scores were transformed into demographically corrected T-scores using established norms. T-scores for each test were then used in as dependent measures in subsequent analyses[68].

Cytokine Assessments

Blood samples were drawn from each participant. After separation, plasma samples were immediately frozen and stored at −80°C. Aliquots were used to measure chemokine and cytokine levels using an xMAP multiplexed bead array immunoassay. This approach permits simultaneous quantification of multiple cytokines in solution by capturing them onto antibody coated spectrally distinct fluorescent microspheres, and measuring fluorescence intensity using the Luminex-100 system (Luminex Corp., Austin, TX). The panel of cytokines used, along with the proposed function of each molecule, is listed in Table 3.

Statistical Analysis

A multivariate ANOVA was performed to examine whether all the measured cytokine concentrations differed between the HIV+ and HIV− groups, with age and sex treated as covariates. Follow-up univariate ANOVA were then performed to test for the differences between HIV+ and HIV− groups for individual cytokines, after correcting for multiple comparisons.

The relationships between HIV clinical variables and plasma cytokine concentrations in the HIV-infected group were next examined via stepwise regression analysis with backward selection. For these analyses, current and nadir CD4, detectable HIV RNA, duration of HIV infection (i.e. years since HIV diagnosis), antiretroviral treatment status, and comorbid HCV infection, were entered as independent measures predicting individual cytokine concentrations in a series of analyses.

In a final set of analyses, the relationship between plasma cytokine concentrations and performance on individual neurocognitive measures were examined. For these analyses, the thirteen cytokines were entered as potential predictors into regression models with the cognitive performance scores treated as the dependent measures. Demographic (age, education), HIV status, HCV status, lifetime substance dependence history (alcohol, opiates, cocaine) were entered into regression analyses as covariates. In each case, final linear regression models were selected by minimizing Akaike Information Criterion (AIC) [75, 76], which balances the model fit and its complexity. Increasing the number of parameters in the models improves their fit to the data, but at a cost of increased complexity. AIC balances the goodness of fit and the number of included covariates by penalizing the number of parameters in the model. The best model is the one with the lowest AIC. This method is more robust than the traditional stepwise selection procedures and produces parsimonious models balancing the goodness of fit and model complexity. To ameliorate the selection of models that might contain non-significant variables, we used a bootstrap procedure as previously described on the results of the initial fit, and only chose the variables for the final models that were selected in more than 70% of the bootstrapped samples[25, 26]. Statistical analyses were done using R-2.9.2 (R Core Development System: http://www.r-project.org).

RESULTS

HIV effects on cytokine concentrations

Significant difference were found between the HIV+ and HIV− groups with respect to overall plasma cytokine concentrations on MANOVA (Wilks' Lambda = .55, F (13, 48) = 2.95, p = .003). Follow-up univariate analyses showed significant group differences on a number of the measures (Table 4). Elevated levels of IP-10 (p = .001) and MIP-1β (p = .03) were found among HIV+ participants compared to controls. In contrast, HIV+ participants had decreased levels of IL-1β (p = .004), IL-6 (p = .003), IFN-γ (p = .002), MCP-1 (p = .04), and TNF-α (p = .003).

Cytokine concentrations as a function of clinical factors

Analysis of the HIV-infected group revealed significant associations among several of the clinical factors and plasma chemokine levels. The results of the regression model for each cytokine are provided in Table 5. HAART treatment status was significantly associated with IL-1β (p = .014). Detectable viral load (p = .027), current CD4 level (p = .029) and HCV status (p = .05) were associated with IL-6. Duration of HIV infection (p = .003) and nadir CD4 (p = .004) were significantly associated with IL-10 levels. HCV status was associated with IL-16 (p = .001). Duration of HIV infection was significantly associated with IL-18 (p = .03). Duration of HIV infection (p = .02), detectable viral load (p = .04), and HCV status (p = .05) were significantly associated with IP-10. Duration of HIV infection (p = .007) and HAART status (p = .03) were significantly associated with TRAIL. HCV status (p = .033) and nadir CD4 (p = .05) were associated with MIP-1β. None of the clinical variables were significantly associated with MCP-1, IFN-γ, IL-8, SDF-1α, or TNF-α concentrations.

Cytokines and cognitive function

Overall, cytokine concentrations were found to be significantly associated with performance on all measures of attention-executive functioning and psychomotor speed that were examined (see Table 6). Six cytokines were retained as significant predictors of Digit Symbol-Coding performance. Reduced performance on Digit Symbol-Coding was associated with elevated IL-16 (p = .0007), IP-10 (p = .02), IFN-γ (p= .02) and reduced IL-1β (p =.04), IL-10 (p=.04), and IL-18 (p = .008) concentrations. Three cytokines were retained as significant predictors of Trail Making performance. Reduced performance on Trail Making-A was associated with elevated IL-16 (p < .0001) and IP-10 (p = .003) and

reduced IL-10 (p=.001) concentrations. Reduced performance on Trail Making-B was associated with elevated IL-6 (p = .040) and reduced IL-10 (p=.01) concentrations. Four cytokines were retained as significant predictors of performance on the interference condition of the Stroop task. Reduced performance on the Stroop task was associated with elevated MIP-1β (p = .044) and reduced IL-18 (p < .001), MCP-1 (p = .007), and TNF-α (p = .003) concentrations. Two cytokines were retained as significant predictors of Symbol Search performance, with reduced scores on this test associated with elevated IP-10 (p = . 02) and decreased TRAIL (p = .05) concentrations. Two cytokines were also retained as significant predictors of Letter-Number Sequencing performance, with reduced scores on this test associated with reduced IL-10 (p = .003) and TRAIL (p = .02) concentrations. IL-16 was retained as a significant predictor of Grooved Pegboard performance, with reduced scores on this test associated with elevated IL-16 (p = .01) concentrations. In these analyses, we also examined the contribution of HIV status to the association between cytokine concentrations and cognitive function. HIV status was only retained as a significant predictor of Letter-Number Sequencing (p = .05).

DISCUSSION

Findings from the current study provide a number of insights into cytokine abnormalities associated with HIV infection and their relationship to neurocognitive function. Plasma cytokine concentrations differed dramatically between HIV-infected and seronegative controls. HIV-infected participants differed from controls on seven of thirteen cytokines that were measured, suggesting robust effects of HIV on plasma cytokine concentrations. While other studies have reported HIV-associated abnormalities involving specific cytokines, this is among the first study to describe such abnormalities on a large panel of cytokines assessed by bead based multiplex assay.

Given that MIP-1β and MCP-1 have been previously implicated in a number of studies of HIV 33, 46, 77[-79], the apparent group differences for these cytokines were expected. Yet, larger effects were actually observed for the interleukins, including IL-1β and IL-6, and also on two cytokines tied to interferon metabolism (IP-10, IFN-γ), suggesting that cytokine abnormalities observed in HIV extend well beyond isolated effects on MIP-1β and MCP-1. This finding provides evidence of significant inflammatory processes occurring in the context of HIV infection. Furthermore, IFN-γ and IP-10 both play important roles in adaptive immune responses to intracellular pathogens, inhibition of viral replication, and IP-10, induced by IFN-γ and TNF-α, is a chemoattractant for activated T cells. Accordingly, the results suggest that complex changes in plasma cytokine function occur in the context of chronic HIV infection.

Analyses of the associations between specific clinical factors and plasma cytokines in the HIV+ group also suggest complex relationships among viral, immunological and other clinical factors and specific cytokine concentrations. Duration of HIV infection and nadir CD4 were among the clinical factors most consistently found to be associated with specific cytokine concentrations. This finding points to the potential importance of chronic infection and also the possibility that the maximal severity of immunological damage incurred at some point in the individual's disease history has long- lasting effects on cytokine function. The presence of currently detectable plasma viral load emerged as a predictor of only IP-10 concentrations, while current CD4 level was not retained as predictor of any cytokine, probably reflecting the fact that as a whole the HIV-infected group had well controlled immunological function.

HAART treatment status was a predictor of only two cytokines (IL-1β and TRAIL). The lack of stronger associations for this clinical variable may reflect the fact that most patients

in the sample were HAART-treated and medically stable. Accordingly, the findings with respect to plasma cytokine concentrations in this study need to be considered as providing evidence regarding the behavior of the cytokines in the context of largely successful antiretroviral treatment. Also, it was not possible to reliably determine the duration of HAART treatment: while current antiretroviral medications were well documented for all participants, the date that particular medications were initiated was not always obtainable. Therefore, it is possible that differences in the duration of HAART could influence effects that were observed. This will need to be examined in future studies.

Somewhat surprisingly, MCP-1 concentrations were not found be significantly associated with any of the viral or immunological factors tied to HIV status, and only nadir CD4 was found to be significantly associated with MIP-1β. The fact that a greater number of HIV clinical variables were not associated with these two cytokines is not entirely clear, but again may relate to the fact that as a group the HIV-infected participants were stable in their antiretroviral treatment and had relatively well constituted immune systems, as reflected by their current CD4 and HIV RNA levels. . Interestingly, the presence of HCV proved to be more strongly associated with several of the cytokines (IL-6, IL-16, MIP-1β) than was HIV status, suggesting the potential importance of this comorbidity among medically stable HIV-infected people.

A primary objective of this study was to examine the relationship between plasma cytokines and neurocognitive functioning. Strong associations were observed between plasma cytokine concentrations and performance on neurocognitive measures. The pattern of cytokine findings tended to be consistent across the neurocognitive measures, supporting the validity of the effects. It was not the case that a specific cytokine always served as the best predictor of neurocognitive function across all tasks. For example, reduced Trail Making performance was associated with elevated IL-16 and IP-10 and reduced IL-10, whereas reduced Stroop performance was associated with elevated MIP-1β, and reduced IL-18, MCP-1 and TNF-α. Yet, the interleukins, in particular IL-10 and IL-16, along with the interferon precursor IP-10, were the cytokines most consistently retained as best predictors of neurocognitive performance. This finding points to potential influence of a broader set of cytokines than MCP-1 and MIP-1β on attention, executive functioning, and psychomotor speed. This is noteworthy since recently considerable emphasis has been directed at examining the influence of MCP-1 and MIP-1β on HIV-associated brain dysfunction.

The association between plasma cytokine concentrations and neurocognitive functioning appears to occur independently of the effects of HIV status to some extent. When HIV status and demographic variables were entered into the statistical models along with the cytokines, HIV was retained as a significant predictor of neurocognitive functioning along with the cytokines for only one neurocognitive measure (Letter-Number Sequencing). This suggests that the general relationships between cytokine concentrations and neurocognitive functioning observed in the study sample existed regardless of HIV status. This raises the possibility that other conditions in addition to HIV are also affecting cytokines in this cohort, and that one needs to extend consideration of factors influencing cytokine concentrations beyond HIV alone. Accordingly, for HIV-infected individuals whose viral load and immunological function are well controlled on HAART, HIV may be one of multiple factors affecting cytokine levels and ultimately their relationship to inflammatory processes and neurocognitive function.

It is noteworthy that TNF-α was found to be reduced among HIV-infected persons in the study compared to the control subjects, and also that elevated TNF-α levels were actually associated with better neurocognitive performance. The reasons for this are not entirely clear, though several past studies have reported that successful HAART treatment is

associated with reduced TNF-α plasma concentration[80, 81]. Past studies have tended to find that elevated TNF-α is associated with AIDS symptoms, including wasting in HIV[82-85], conditions that were not present in the vast majority of cases in our sample. Additionally, TNF-α levels for all subjects were within the clinically normal range. Therefore, the somewhat counterintuitive effects observed with respect to TNF-α in the current study may reflect beneficial HAART effects and the fact that fact that most participants were not symptomatic.

In summary, the results of this study demonstrate that plasma cytokine concentrations differ between HIV-infected and seronegative individuals, and that these differences extend to a relatively broad range of cytokines beyond MCP-1 and MIP-1β, in particular the interleukins. The HIV and control subjects in this study were carefully matched, not only in basic demographics, but also with respect to their overall socioeconomic characteristics, as they largely came from the same community cohort, therefore minimizing the confounding effects of demographic and clinical factors. A number of clinical factors related to HIV disease status are associated with concentrations of specific cytokines. Most notably, cytokine concentrations were found to be strongly predictive of neurocognitive performance across a range of tests of attention, executive functioning, and psychomotor speed. Yet, the association between cytokines and neurocognitive functioning is not entirely attributable to the effects of HIV, suggesting that further exploration of the influence of HIV in relationship to other comorbidities and risk factors is warranted. Ultimately, it appears that complex interactions among multiple cytokines occur in the context of HIV infection and that these multiple markers should be considered when examining the affect of systemic inflammation on neurocognitive function. We did not obtain CSF from participants in this study. It is possible that CSF levels of cytokines and HIV viral load could provide stronger biomarkers of brain dysfunction. Future studies are needed to test this possibility and to achieve greater understand of the alterations in cytokines concentrations occurring over time as a function of chronic infection, aging, and HAART treatment history.

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Table 1

Neuropsychological measures and associated cognitive functions

Grooved Pegboard[65, 66]	Motor skills
Stroop Color and Word Test[64]	Attention/executive function
Trail Making Test A[63]	Processing speed
Trail Making Test B[63]	Processing speed/executive function
Digit Symbol-Coding[67]	Processing speed/flexibility
Letter-Number Sequencing[67]	Attention/working memory
Symbol Search[67]	Processing speed

Table 2

Demographic and clinical characteristics of participants

	HIV+ (n=30)	HIV− (n=34)
Age (years)	44.8 (9.06)	46.1 (15.95)
Education (years)	12.2 (2.09)	14.0 (3.44)
% Male	63.3	52.9
% Caucasian	40.0	76.5
% Current HCV	30.0	5.9
Current CD4 (cells/μl)	463.9 (284.56)	
Nadir CD4 (cells/μl)	168.6 (130.76)	
Duration of HIV infection (years)	13.1 (7.06)	
% Undetectable HIV RNA	69.0	
% HAART	80.0	

Table 3

Cytokines Assessed In Study

Cytokine/Chemokine	Abbreviation	Function
Interleukin-1-Beta	IL-1β	Produced by activated macrophages; mediates inflammatory responses, cell proliferation, apoptosis. Induces Cox-2 in CNS, causing inflammatory pain
Interleukin-6	IL-6	Secreted by T cells and macrophages; triggers inflammation, acute phase response, fever. Anti-inflammatory effects include inhibiting TNF-α and IL-1, and activating IL-1ra and IL-10.
Interleukin-8	IL-8	Made by macrophages and some epithelial and endothelial cells; Role in innate immune response. Major role in chemotaxis of neutrophils. Also mediates inflammatory response and angiogenesis.
Interleukin-10	IL-10	Produced by monocytes. Pleiotropic cytokine. As an anti-inflammatory cytokine, it inhibits macrophage and dendritic cell function, suppresses TNF-α. Acquires pro-inflammatory activity during immune response with IFN-α stimulation.
Interleukin-16	IL-16	Secreted by lymphocytes. Pleiotropic cytokine. Functions as a chemoattractant (CD4+ cells), modulates T cell activation, and inhibits HIV replication.
Interleukin-18	IL-18	Produced by macrophages and monocytes. Pro-inflammatory cytokine interacts with IL-12 to induce cell-mediated immune response with microbial infection and LPS, inducing severe inflammatory reactions. Stimulates NK and T cell release of IFN-γ, which activates macrophages. Inhibits IL4-dependent IgE, enhances B cell production.
Interferon gamma-soluble cytokine	IFN-γ	Produced by innate NK cells, acquired antigen-specific cytotoxic CD4+ and effector CD8+ T cells. Activates macrophages and critical for innate and adaptive immune responses to intracellular pathogens, tumor control, and inhibition of viral replication.
Interferon-inducible protein-10	IP-10	Produced by various cell types including monocytes, endothelial cells, fibroblasts, keratinocytes. Induced by IFN-γ and TNF-α. Chemoattractant for activated T cells.
Macrophage inflammatory protein-1-beta	MIP-1β	Produced by macrophages. CCL4 chemokine that generates local inflammatory responses, induces superoxide production by neutrophils. Chemotactic activity for lymphocytes, macrophages, NK cells, and monocytes with inflammation; down-regulates CCR5, inhibiting HIV-1 blocking.
Monocyte chemoattractant protein-1	MCP-1	Expressed in monocytes, vascular endothelial cells, smooth muscle cells. CCL2 chemokine, induces monocyte attraction, and degranulation of basophils with histamine release. Induced by IL-1, TNF-α, PDGF, TGF-β, and LIF
Stromal cell-derived factor-1-alpha	SDF-1α	Expressed ubiquitously, except in blood cells. Small cytokine member of CXCL12 family of chemokines. Activates leukocytes due to strong chemotactic effects. Induced by pro-inflammatory stimuli, e.g. TNF-α and IL-1β.
Tumor necrosis factor related apoptosis-inducing ligand	TRAIL	Expressed broadly in tissues. Cytokine induces proapoptotic caspase activity by up-regulating pro-apoptotic Bcl proteins. Causes apoptosis in hepatocytes, neural cells, and thymocytes
Tumor Necrosis factor-alpha	TNF-α	Secreted by macrophages, monocytes, neutrophils, T cells, NK cells after stimulation with LPS. CD4+ cells secrete TNF-α. Also made by astrocytes, microglial cells, smooth muscle cells, and fibroblasts. Mediates systemic inflammation, inhibits viral replication, and inhibits tumorigenesis.

Table 4

Plasma cytokine levels of HIV-infected and seronegative participants

Cytokine	HIV+				HIV−				p	Partial η^2
			95% Confidence Interval				95% Confidence Interval			
	Mean	SD	Lower	Upper	Mean	SD	Lower	Upper		
IFN-γ	2.45	0.61	2.22	2.68	4.65	3.90	3.29	6.01	**0.002**	0.143
IL-1β	4.15	0.48	3.97	4.33	5.50	2.61	4.59	6.41	**0.004**	0.129
IL-6	4.77	2.32	3.90	5.63	7.79	4.90	6.08	9.50	**0.003**	0.134
IL-8	13.88	4.44	12.22	15.54	13.10	4.19	11.64	14.57	0.549	0.006
IL-10	15.67	3.51	14.36	16.98	19.15	10.46	15.50	22.80	0.060	0.058
IL-16	73.23	29.77	62.12	84.35	79.49	41.54	64.99	93.98	0.563	0.006
IL-18	55.32	31.85	43.42	67.21	43.40	26.43	34.17	52.62	0.129	0.038
IP-10	727.50	729.88	454.96	1000.04	248.35	344.09	128.29	368.41	**0.001**	0.162
MCP-1	98.43	64.15	74.48	122.39	136.72	75.26	110.46	162.98	**0.044**	0.066
MIP-1β	69.57	61.96	46.43	92.70	42.44	35.07	30.20	54.68	**0.034**	0.073
SDF-1α	22.95	6.53	20.51	25.39	26.31	10.60	22.61	30.01	0.140	0.036
TNF-α	4.58	0.86	4.26	4.91	5.60	1.74	4.99	6.21	**0.003**	0.136
TRAIL	24.68	9.68	21.07	28.30	25.85	7.94	23.08	28.62	0.549	0.006

Abbreviations: See table 3. Significant differences at $p<.05$ are indicated in bold.

Table 5

Cytokine levels as a function of demographic and clinical variables

	t	p	R
IFN-γ			.447
Sex	2.548	.017	
IL-1β			.457
HAART	−2.621	.014	
IL-6			.616
HCV	2.066	.050	
HIV RNA	2.352	.027	
Current CD4	2.315	.029	
IL-10			.634
HIV Duration	3.252	.003	
Nadir CD4	3.133	.004	
IL-16			.574
HCV	3.571	.001	
IL-18			.410
HIV Duration	2.293	.030	
IP-10			.848
HCV	2.056	.05	
HIV Duration	2.498	.021	
HIV RNA	2.216	.038	
MIP-1β			.479
HCV	2.261	.033	
Nadir CD4	2.011	.05	
TRAIL			.553
HIV Duration	2.941	.007	
HAART	−2.314	.029	

Results of stepwise regression analysis with backward selection. Only predictors selected in the final model with $p < .05$ are reported. *R* values are for the whole model fit. Cytokine abbreviations: See Table 3.

Table 6

Cognitive test performance as a function of cytokine levels.

	β	*p*	Adjusted R^2	*p*
Grooved Pegboard Worse Hand			0.08	0.01
IL-16	−0.08	0.01		
Stroop Interference			0.34	<0.0001
IL-18	0.09	0.0004		
MCP-1	0.02	0.007		
MIP-1β	−0.03	0.044		
TNF-α	2.02	0.003		
Trail Making Test A			0.31	<0.0001
IL-10	0.42	0.001		
IL-16	−0.14	<0.0001		
IP-10	−0.006	0.003		
Trail Making Test B			0.39	<0.0001
IL-10	0.36	0.01		
IL-16	−0.06	0.04		
WAIS-III Digit Symbol-Coding			0.43	<0.0001
IFN-γ	−1.82	0.02		
IL-1β	2.34	0.04		
IL-10	0.26	0.04		
IL-16	−0.06	0.007		
IL-18	0.07	0.008		
IP-10	−0.003	0.02		
WAIS-III Letter-Number Sequencing			0.25	0.0009
IL-10	0.38	0.003		
TRAIL	0.23	0.02		
WAIS-III Symbol Search			0.23	0.002
IP-10	−0.004	0.02		
TRAIL	0.23	0.05		

Regression models selected using Akaike's information criterion. Demographic, clinical, and cytokine variables were entered as predictors; only cytokines selected in the final model with p <.05 are reported. Adjusted R^2 values are for the whole model fit. Abbreviations: WAIS-III, Wechsler Adult Intelligence Scale-Third Edition; Stroop, Stroop Color and Word Test; Cytokine abbreviations: See Table 3.