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Social isolation is linked to inflammation in aging people with HIV and uninfected individuals

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Abstract

Background: Even in the era of suppressive antiretroviral therapy, people with HIV (PWH) suffer greater exposure to inflammation than their uninfected peers. Although poor social support and social isolation have been linked to systemic inflammation in the general population, it is not known if this is true also among PWH.

Methods: People with and without HIV infection were enrolled in a community-based, single center study. Primary predictors were the Medical Outcomes Study (MOS) Social Support Survey and outcomes were a panel of inflammatory biomarkers (ICAM-1, MCP-1, IL-6, IL-8, IP-10, CRP, D-Dimer, VEGF, sCD14 and uPAR) in blood plasma and cerebrospinal fluid (CSF).

Results: PWH had worse Positive Social Support ($p = 0.0138$) and Affectionate Support ($p = 0.0078$) than did HIV− individuals. A factor analysis was used to group the biomarkers into related categories separately for each fluid. Levels of three of the four Plasma Factors were significantly higher in in PWH than HIV− (ps = 0.007, 0.001 and 0.0005, respectively). Levels of one of the three CSF Factors also were significantly higher in PWH than HIV− $p = 0.0194$). In the combined PWH and HIV− cohort, poorer social support was associated with higher levels of a factor in plasma loading on MCP-1, IL-8 and VEGF ($p = 0.020$), and with a CSF factor loading on MCP-1 and IL-6 ($p = 0.006$).

Conclusion: These results suggest that enhancing social support might be an intervention to reduce inflammation and its associated adverse outcomes among PWH.

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Author Contributions

Dr. Ellis conceived the study design, performed the statistical analyses and drafted the manuscript. All authors reviewed the manuscript and contributed to writing.

Conflict of Interest

The authors report no conflicts of interest.

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Introduction

Mounting evidence reveals that social support is beneficial for prevention and management of HIV disease[1-4].Signs of poor social support, including social isolation and loneliness, are common in people living with HIV, particularly in older adults and ethnic minorities[5]. Poor social support is associated with poor health outcomes among PWH, including faster progression to AIDS[6], functional impairment[7,8], poor health-related quality of life[9], poor retention in care[10] and higher rates of mortality[11]. In some clinical populations, social isolation has been linked to systemic inflammation [11,12]. However, the link between poor social support and systemic inflammation has not been studied among PWH and therefore it is not known whether the association may be stronger in them than in other populations. Even in the setting of viral suppression with antiretroviral therapy (ART), PWH have persistently elevated levels of inflammation biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP). Increased inflammatory biomarkers are, in turn, associated with adverse health outcomes such as myocardial infarction and even death [13-17]. Persistent inflammation in virally suppressed PWH also affects the central nervous system (CNS), where microglia and astrocytes are chronically activated [18,19], producing neurotoxic cytokines that can contribute to cognitive impairment, depression and other adverse outcomes. To our knowledge, the relationship between poor social support and neuroinflammation as indexed by cerebrospinal fluid (CSF) biomarkers has never been reported. Identification of poor social support as a driver of persistent inflammation in PWH would be important because it is potentially modifiable and could be improved with intervention. As such, we evaluated the hypothesis that poor social support would be associated with elevated levels of inflammatory biomarkers, both in blood and in CSF.

Methods

Participants

PWH and HIV− participants recruited from community sources were prospectively enrolled in cohort studies at the University of California, San Diego. Inclusion criteria included HIV seropositive or seronegative, consented to lumbar puncture and phlebotomy, and had a sufficient volume of CSF and plasma in storage at −80°C to perform assays. Exclusions included abuse or dependence of methamphetamine, alcohol and other substances within the past 18 months; significant CNS confounding conditions such as history of AIDS-defining opportunistic infection of the CNS; traumatic brain injury resulting in permanent neurological deficits; and major, active psychiatric disorders such as schizophrenia. All participants signed informed consent documents approved by the local IRB.

Clinical Evaluations

The Medical Outcome Study Social Support Survey (MOS-SSS)[20] consists of 19 items (item 2 to item 20) measuring the functional aspects of perceived social support and one additional item (item 1) assessing the number of close relatives and friends (item 1 was not included in data analysis). The instrument is easy to administer to chronically ill patients and demonstrates high convergent validity, discriminant validity, Internal-consistency, reliability and one-year stability. The MOS-SSS measures four domains of social support including

tangible/instrumental support, emotional-informational support, positive social interactions and affectionate support [21]. An additional item queries whether the person has "Someone to do things with to help you get your mind off things." Participants rated the MOS-SSS items using a five-point Likert rating scale ranging from (1) none of the time to (5) most of the time. The mean scores of the overall scale and four subscales were then transformed to a 100-point scale using the formula: Transformed score = [(observed score – minimum possible score)/(maximum possible score – minimum possible score)] × 100.[20] A higher score indicates higher level of self-reported social support. Current mood was assessed using the Beck Depression Inventory (BDI)-II (1), a widely used 21-item self-report inventory measuring the severity of depressed mood.

Biomarkers

Our selection of plasma biomarkers was informed by previous studies linking them and other inflammatory factors to lack of social support and stress: soluble tumor necrosis factor alpha type II (sTNFRII)[22,23], d-dimer, interleukin-6 (IL-6)[24,25], C-reactive protein (CRP)[26,27], monocyte chemoattractant protein type I (MCP-1)[28], soluble CD14 (sCD14) [29], IP-10[30], uPAR, IL-8[31] and VEGF[32,33]. Biomarkers were measured in plasma and CSF using standard immmunoassays.

Additional clinical and laboratory assessments

Comprehensive neuromedical assessments were performed. These assessments included vital signs, neurological and physical examination, collection of medical history including ARV regimen, and collection of blood and CSF. HIV serostatus was documented by ELISA and confirmed by Western blot. Routine clinical assays, such as blood CD4+ T-cell count and CSF total protein, were measured in the Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory at the University of California, San Diego Medical Center. HIV RNA levels were measured in CSF and plasma by real time polymerase chain reaction with a lower quantification limit of 50 copies/mL (Abbott Diagnostics, Des Plaines, Illinois, USA).

Statistical Analyses

Demographics, medical history, and HIV disease characteristics were summarized using means and standard deviations, medians and interquartile ranges or counts and percentages as appropriate. Demographic data were compared between PWH and HIV− individuals using independent samples t-test for continuous variables and Fisher's exact test for categorical variables. Log_{10} transformations were applied to biomarker measures to improve symmetry and normality of distributions. Exploratory factor analyses with oblique Varimax rotation were employed to reduce the dimensionality of the biomarkers, grouping them into related categories. All biomarkers studied were allowed to enter the factor analysis. Factors with Eigenvalues >= 1 were included. We then examined Pearson correlations between overall social support variable and the plasma and CSF inflammation biomarker factors. A Bonferroni correction for multiple comparisons was applied (p = 0.05/the number of factors). Secondary analyses are presented for each of the social support subcomponents. Separate multivariable regressions were used to assess the interaction effects between HIV serostatus and Factor levels. Demographics (i.e., age and ethnicity) were included in

multivariable models and retained as covariates if p-value was less than 0.2 in backward model selection. The results were considered statistically significant at the 5% alpha level. JMP Pro version 14 was used for all analyses.

Results

As shown in Table 1, participants were 69 PWH and 87 HIV−, 31.4% female with a mean (SD) age of 44.9 (14.5) years. Approximately half (51.9%) were non-Hispanic white, 27.6% Hispanic, 14.1% Black and 6.4% other ethnicities. Among PWH, 55 (80.9%) were virally suppressed. Table 1 compares PWH and HIV− participants on demographic and disease variables and on social support variables. The groups were well-matched on age and ethnicity, but the proportion of women in the HIV− group was much larger. Social support was worse in PWH than HIV−; this was marginal for Overall Social Support, but significant for Affectionate ($p = 0.0078$) and Positive support ($p = 0.0138$). Overall Social Support was poorer with increasing age among HIV− ($r = -0.268$, $p = 0.0122$), but not PWH ($r = -0.00996$, $p = 0.935$). Ethnicity and sex were not significantly associated with Overall Social Support in either group.

Plasma Factor Analysis

The plasma factor analysis (N=156) yielded four factors that accounted for 68.8% of the variance, with CRP, IL-6 and D- dimer loading onto Factor 1; sTNFR-II, IP-10 and uPAR loading onto Factor 2; MCP-1, IL-8 and VEGF loading onto Factor 3; and sCD14 loading onto Factor 4. Levels of Plasma Factors 2-4 were significantly higher in in PWH than HIV− (Factor 2 mean [sd], 0.152 [0.896] vs −0.210 [0.850]; $p = 0.007$; Factor 3, 0.0242 [0.840] vs. −0.424 [0.898]; $p = 0.001$; Factor 4, 0.0101 [0.607] vs. −0.466 [1.0455]; $p = 0.0005$). Factor 1 levels did not differ significantly between the two groups (0.413 [0.101] vs −0.160 [0.093]; $p = 0.0665$).

Table 2 shows correlations of the overall support index and subscales with the plasma biomarker factors. Worse overall social support and each of the subscales was associated with higher levels of Factor 3. None of the other factors was associated with social support. None of the social support variables interacted with HIV serostatus in predicting plasma inflammation factors, indicating that associations between inflammation and social support were not significantly different for the two groups. In a multivariable model, age and its interaction with Overall Social Support also was non-significant.

Potential confounds – plasma analysis.—Increasing age was related to higher levels of Factor 1 in both PWH ($r = 0.411$, $p = 0.0004$) and HIV− participants ($r = 0.293$, $p = 0.006$). Factors 2-4 were not significantly related to age. Among HIV− participants, women had higher Factor 1 levels than men ($p = 0.0002$), but lower Factor 3 levels than men ($p = 0.0041$). Among PWH, there were no sex differences. None of the factors was related to ethnicity. Older individuals had poorer Overall Social Support among HIV− ($r = -0.268$, $p = 0.0122$), but not PWH ($r = -0.0001$, $p = 0.935$). Lack of plasma viral suppression (19.1% of PWH) was related to higher levels of plasma Factor 2 ($p = 0.0012$) and Factor 4 ($p = 0.0078$), but not significantly related to the other factors. Higher current CD4 was associated with higher levels of Factor 1 ($r = 0.223$; $p = 0.0250$) and lower levels of Factor 4 ($p = 0.202$;

r = 0.0427). Lower nadir CD4 predicted higher levels of Factor 2 (r = −0.286; p = 0.0034). Current and nadir CD4 were not related to the other factors. In a multivariable model predicting Factor 3 levels from Overall Social Support and age, Social Support remained significant (p = 0.0372), while age was not. Sex was not significant in any multivariable models. Because a subtype of major depressive disorder has been associated with inflammation, we also modeled the potential contribution of depressive mood to the plasma inflammation factors. In a multivariable model predicting plasma Factor 3, including Overall Social Support, BDI-II score and their interaction, neither the main effect of BDI-II, nor the interaction term was significant, and their inclusion did not alter the statistical significance of social support (p = 0.0193).

CSF Factor Analysis

A subset of 43 PWH and 34 HIV− had CSF available for analysis. The CSF Factor analysis (N=86) yielded 3 factors accounting for 63.2% of the variance, with uPAR, sCD14 and sTNFR-II loading onto Factor 1; MCP-1 and IL-6 loading onto Factor 2, and D-Dimer and CRP loading onto Factor 3. Levels of Factor 1 were significantly higher in PWH than HIV− (p = 0.0194).

Table 3 shows the correlation matrix for the social support variables and the CSF factors for PWH and HIV− together. Poorer social support was significantly associated with higher levels of Factor 2 for the Overall Support Index and for all but one of the support subscales. Factors 1 and 3 were not significantly associated with any of the social support measures. In a multivariable model, Overall Social Support was significantly associated with CSF Factor 2, but HIV serostatus and the interaction were not.

To evaluate the relative importance of CSF versus plasma inflammation with respect to social support, we performed a multivariable regression predicting the Overall Support Index from Plasma Factor 3 and CSF Factor 2. CSF Factor 2 retained significance in the model (p = 0.00646), while Plasma Factor 3 did not (p = 0.203). The interaction term was non-significant.

Potential confounds – CSF analysis.—In the combined PWH and HIV− sample, older individuals had higher levels of CSF Factor 1 (r = 0.461, p < 0.0001); age was not related to the other CSF factors. Sex and ethnicity were not significantly related to any of the factors. Older age was associated with poorer Overall Social Support (r = −0.168, p = 0.0355). None of the other demographic variables was significantly related to Overall Social Support. In a multivariable model predicting Factor 2 levels from age and Overall Social Support, the latter remained significant (p = 0.00392), whereas age was not significant (p = 0.0843). Again, in a multivariable model, there was no interaction between HIV serostatus and Overall Social Support in predicting Factor 2 levels. Because of the large difference in the proportions of women between PWH and HIV−, we included sex in a multivariable model predicting Factor 2 levels from serostatus, sex and Overall Social Support. The interaction term (sex X Social Support) was non-significant, and Overall Social Support remained significant in the model (p = 0.0118), while sex was not (p = 0.463). PWH with lower current CD4 counts had higher levels of CSF Factor 2 (r = 0.414, p = 0.0058), but not the

other CSF factors. Nadir CD4 was not related to any of the factors. In a multivariable model containing current CD4, Overall Support and their interaction, both Overall Support ($p = 0.0170$) and CD4 ($p = 0.0330$) were significant; the interaction was not. Only one participant had a detectable CSF viral load.

As noted above, a subtype of major depressive disorder has been associated with inflammation. Thus, we also modeled the potential contribution of depressive mood to inflammation. In multivariable models predicting the CSF factors from Overall Social Support BDI-II score and their interaction, neither BDI-II nor its interaction with social support was a significant predictor of any of the CSF inflammation factors, and did not alter the statistical significance of Overall Social Support index.

Discussion

Our finding that poorer social support correlated with higher plasma inflammatory biomarkers is consistent with the prior literature [12,23,34,35]. However, no previous reports of CSF inflammation markers were available for comparison. Neuroinflammation as indexed by CSF biomarkers was more strongly related to social support than systemic inflammation as indexed by plasma biomarkers. The relationships we found were robust to consideration of potential confounds including demographics, viral suppression and depressed mood. The associations of social support with systemic and CNS inflammation may be particularly important in the context of HIV, where chronic inflammation occurs despite viral suppression on ART. Both poorer social support and inflammation in HIV are linked to adverse outcomes including cardiovascular disease, neurocognitive impairment and death [13-16,3637].

As outlined in the Methods section, our selection of biomarkers to assay was informed by previous studies linking them to poorer social support. Additionally, the biomarkers selected have been linked previously to HIV disease progression, viral load and mortality. For example, CRP, IL-6 and d-dimer (plasma Factor 1) have been shown to be independent predictors of mortality[383940] and HIV disease progression[40,41] . sTNFRII levels (Factor 2) were reported to be significantly higher in patients with more advanced HIV disease as indexed by CD4 count[42] , and higher levels were associated with increased mortality[43] . Increased IP-10 levels can promote HIV disease progression, manifested as loss of CD4+ T cells and increased viral loads [44,45]. Serum sUPAR levels predicted early death in one study[46]. Plasma levels of MCP-1 (Factor 3) are increased in patients with higher virus load[47]. A significant negative correlation of plasma levels of IL-8 with CD4 counts (cells/μL) was observed in HIV−1 infected ART naïve subjects and IL-8 levels positively correlated with viral load in ART treated children[48] . CD4 counts and viral loads were also significantly associated with serum IL-8 concentrations[49] . sCD14, a marker of monocyte response to LPS, is an independent predictor of mortality in HIV infection[50] , and high sCD14 levels during primary HIV−1 infection predicted more rapid disease progression[51] . Additionally, increased levels of MCP-1 in the CNS and CSF (CSF Factor 2 in this study) occured in HIV-encephalitis[52-54], which is in turn associated with high mortality and advanced HIV disease.

We used factor analysis to summarize the various biomarkers of inflammation. Factor analysis is a statistical method used to describe variability among observed, correlated variables in terms of a potentially lower number of unobserved variables called factors. Thus, factor analysis is a method for dimensionality reduction and can help control false discovery. It is important to check the identified factors against known physiological relationships. Following on this, we found that the biomarker factor patterns emerging from our analyses were consistent with previous literature. For example, the pro-inflammatory cytokine IL-6 stimulates the production of C-reactive protein (plasma Factor 1) in the liver [55]. In one study of PWH, both IL-6, CRP and D-dimer (see plasma Factor 1 and CSF Factor 3) were intercorrelated and each was associated with an increased risk of cardiovascular disease (CVD) independent of other CVD risk factors [56]. IL-6, CRP and ICAM-1 are frequently co-upregulated[57]. MCP-1 and IL-8 (plasma Factor 3) together participate in the adhesion of monocytes to vascular endothelium[58]. suPAR levels have been associated with IP-10 and sTNFR-II (plasma Factor 2)[59]. In another study, after carotid artery occlusion, secretion of the cytokines IL-6, and TNF-α led to an upregulation of ICAM-1 on the vascular endothelium, which promotes leukocyte migration across the BBB[60]. In a study of subarachnoid hemorrhage there were strong correlations between CSF levels of IL-6 and MCP-1 (CSF Factor 2)[61]. In HIV infection, sCD14 and sTNFR levels (CSF Factor 1) were highly correlated[62]. Together, these observations suggest that the factors we identified represent consistent patterns of inflammation.

The elevated inflammation factors associated with social support differed partially between plasma (MCP-1, IL-8 and VEGF) and CSF (MCP-1 and IL-6). MCP-1 was common between the two. In one study, lonelier diabetics without HIV had raised plasma MCP-1 concentrations following a stressful stimulus[63]. In another, plasma MCP-1 levels were higher with stress in patients with a recent myocardial infarction[64]. Stimulated production of interleukin-8 was higher in participants with lower levels of social support[31], but CSF was not studied in this report. Similarly, women with ovarian carcinoma who reported lower levels of social well-being had higher levels of VEGF[33].

As is true for any cross-sectional study, our data cannot determine causality, nor can it determine determine the direction of causality if it does exist — in other words, whether lack of social support causes inflammation or inflammation leads – possibly indirectly, through effects on cognition or other aspects of behavior -- to social isolation. Indeed, it is conceivable that both social support and inflammation may be linked to a third, unobserved variable. We did not see evidence that the links were attributable to depressed mood. Causality may be informed by future longitudinal studies that can evaluate whether changes in social support may relate to changes in systemic inflammation. Several observations deserve consideration here. Inflammation, like pain, produces physical withdrawal; similarly, inflammation might lead to social withdrawal. In one study, an inflammatory challenge (endotoxin) led to higher levels of perceived social disconnection in healthy volunteers[65]. Alternatively, lack of social support might trigger brain pathways involved in the processing of physical pain. Thus, activation of brain regions associated with the salience of pain and pain-related distress -- the dorsal anterior cingulate cortex, insula and ventral prefrontal cortex -- show similar patterns of activation in paradigms designed to elicit social

pain through social exclusion[66,67]. Additionally, cutaneous heat pain sensitivity is associated with distress reported after a social exclusion paradigm[48].

Because of the importance of social cooperation to individual success during human evolution, it is believed that social connectedness co-opted pre-existing brain systems responsible for processing physical pain[68]. By triggering pain systems in the brain, social isolation became an unpleasant experience to be avoided. If it could not be avoided, similar to what happens in chronic pain, inflammation resulted.

This study is limited by the relatively small cohort size, particularly for CSF, and by the cross-sectional design, the imbalance of males and females between PWH and the HIV− group, by inability to control for comorbid medical illness, and by the limited number of biomarkers assessed. The study was under-powered for testing interactions.

These results provide a springboard for future research on the mechanisms linking social support and inflammation. For example, a pilot study might be performed to assess whether social support interventions might reduce inflammation, possibly ameliorating its adverse health consequences, especially in PWH. An important next step might be a randomized clinical trial to determine whether interventions leading to improved social functioning and social satisfaction in PWH would result in reduced inflammation. On the other hand, if inflammation drives social isolation, then knowing which specific inflammatory mediators are critical might lead to targeted anti-inflammatory therapies to treat this condition.

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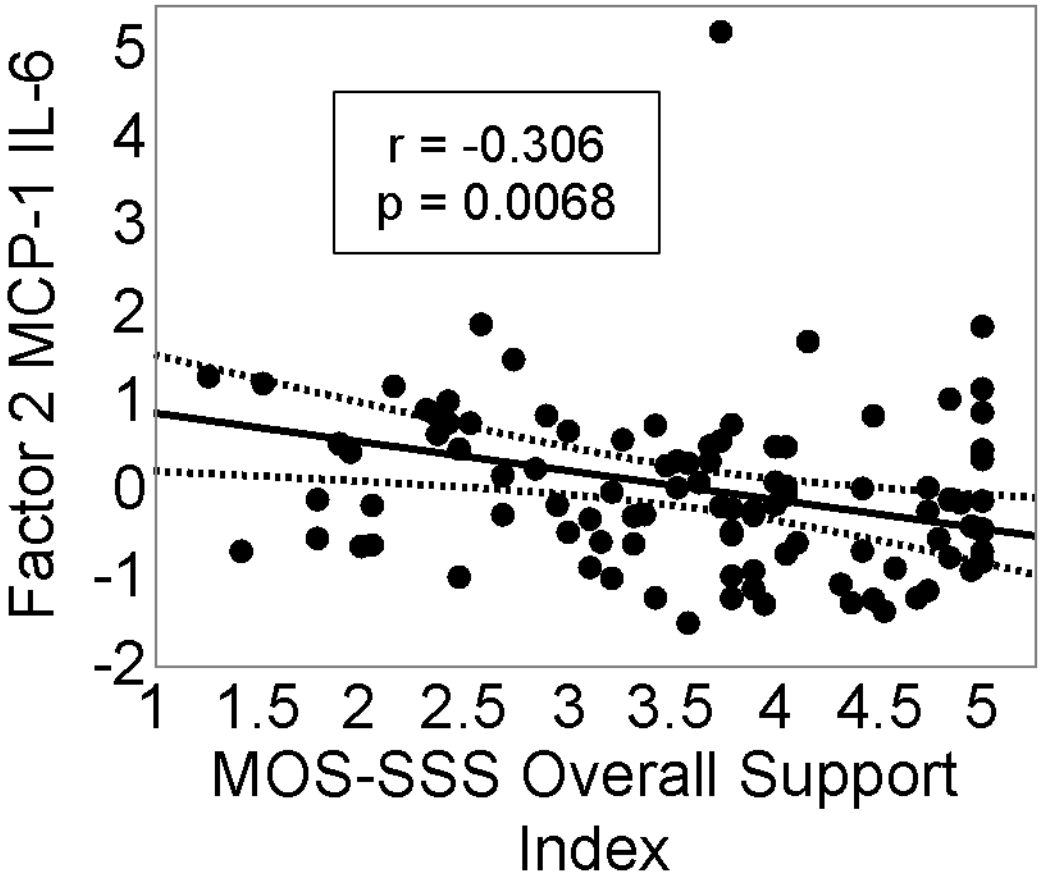

Figure 1.

Table 1.

Demographics, social support and disease variables by HIV status for participants in the plasma factor analysis.

	HIV−	PWH	p
N	87	69	--
Age years (mean, SD)	44.6, 15.9	45.2, 12.6	0.79
Sex female (N, %)	45, 51.7	4, 5.8%	<0.0001
Ethnicity non-Hispanic white (N, %)	44, 50.6	37, 53.6%	0.705
Hispanic	20, 23.0%	23, 33.3%	--
Black	15, 17.2%	7, 10.1%	--
Other	8, 9.20%	2, 2.90%	--
CD4 nadir cells/uL (median; IQR)	--	297; 156, 434	--
CD4 current cells/uL (median; IQR)	--	640; 500, 842	--
Virally suppressed (N, %)	--	55, 80.9%	--
Overall Social Support (mean, SD)	3.94, 0.95	3.66, 0.96	0.0673
Tangible (mean, SD)	3.53, 1.27	3.30, 1.27	0.282
Overall (mean, SD)	3.99, 1.25	3.45, 1.25	0.0673
Tangible (mean, SD)	4.18, 1.01	3.78, 1.01	0.282
Affectionate (mean, SD)	4.08, 1.05	3.77, 0.99	0.0078
Positive Social (mean, SD)	4.02, 0.91	3.86, 0.94	0.0138
Additional item (mean, SD)	3.94, 0.95	3.66, 0.96	0.0598
Educational/Inform (mean, SD)	3.53, 1.27	3.30, 1.27	0.278

Table 2.

Demographics, social support and disease variables by HIV status for participants in the CSF factor analysis

	HIV−	PWH	p
N	34	43	--
Age years (mean, SD)	45.4, 14.2	44.2, 13.7	0.703
Sex female (N, %)	17, 50.0%	3, 6.98%	<0.0001
Ethnicity non-Hispanic white (N, %)	18, 52.9%	16, 47.1%	0.418
Hispanic	9, 26.4%	17, 39.5%	--
Black	5, 14.7%	3, 6.98%	--
Other	1, 2.94%	2, 4.65%	--
CD4 nadir cells/uL (median; IQR)	--	297; 156, 434	--
CD4 current cells/uL (median; IQR)	--	640; 500, 842	--
Virally suppressed (N, %)	--	55, 80.9%	--
Overall Social Support (mean, SD)	3.94, 0.95	3.66, 0.96	0.0673
Tangible (mean, SD)	3.53, 1.27	3.30, 1.27	0.282
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Affectionate (mean, SD)	4.08, 1.05	3.77, 0.99	0.0078
Positive Social (mean, SD)	4.02, 0.91	3.86, 0.94	0.0138
Additional item (mean, SD)	3.94, 0.95	3.66, 0.96	0.0598
Educational/Inform (mean, SD)	3.53, 1.27	3.30, 1.27	0.278

Table 3.

Correlations of the Overall Support Index and its component scores with plasma inflammation factors.

Variable	by Variable	r	5%ile	95%ile	p
Overall Support Index	Factor 1 CRP IL-6 D-dimer	−0.063	−0.218	0.095	0.434
	Factor 2 sTNFR-II IP-10 uPAR	−0.053	−0.209	0.105	0.508
	Factor 3 MCP-1 IL-8 VEGF	**−0.186**	**−0.333**	**−0.030**	**0.020**
	Factor 4 sCD14	−0.096	−0.249	0.062	0.235
Tangible Support	Factor 1 CRP IL-6 D-dimer	−0.072	−0.226	0.086	0.373
	Factor 2 sTNFR-II IP-10 uPAR	0.043	−0.115	0.199	0.593
	Factor 3 MCP-1 IL-8 VEGF	−0.167	−0.316	−0.010	0.037
	Factor 4 sCD14	−0.034	−0.191	0.123	0.670
Affectionate Support	Factor 1 CRP IL-6 D-dimer	−0.056	−0.211	0.102	0.490
	Factor 2 sTNFR-II IP-10 uPAR	−0.141	−0.292	0.016	0.078
	Factor 3 MCP-1 IL-8 VEGF	−0.180	−0.328	−0.023	0.025
	Factor 4 sCD14	−0.120	−0.272	0.038	0.136
Positive Social Support	Factor 1 CRP IL-6 D-dimer	−0.052	−0.207	0.106	0.520
	Factor 2 sTNFR-II IP-10 uPAR	−0.090	−0.243	0.069	0.266
	Factor 3 MCP-1 IL-8 VEGF	**−0.193**	**−0.340**	**−0.037**	**0.016**
	Factor 4 sCD14	−0.050	−0.206	0.108	0.535
Additional Item	Factor 1 CRP IL-6 D-dimer	−0.096	−0.249	0.063	0.235
	Factor 2 sTNFR-II IP-10 uPAR	−0.080	−0.235	0.078	0.318
	Factor 3 MCP-1 IL-8 VEGF	**−0.204**	**−0.350**	**−0.049**	**0.011**
	Factor 4 sCD14	−0.058	−0.213	0.100	0.470
Emotional/Informational Support	Factor 1 CRP IL-6 D-dimer	−0.043	−0.199	0.115	0.595
	Factor 2 sTNFR-II IP-10 uPAR	−0.040	−0.196	0.118	0.618
	Factor 3 MCP-1 IL-8 VEGF	−0.144	−0.294	0.014	0.074
	Factor 4 sCD14	−0.122	−0.274	0.036	0.128

Corrected for multiple comparisons, significant if p <= 0.0125. **Bold** indicates significant correlation.

Table 4.

Correlations of the Overall Support Index and its component scores with CSF inflammation factors.

Variable	by Variable	r	5%ile	95ile%	p
Overall Support Index	Factor 1 uPAR sCD14 sTNFR-II	−0.051	−0.271	0.176	0.644
	Factor 2 MCP-1 IL-6	**−0.294**	**−0.486**	**−0.075**	**0.006**
	Factor 3 D-Dimer CRP	0.140	−0.087	0.353	0.200
Tangible Support	Factor 1 uPAR sCD14 sTNFR-II	0.076	−0.151	0.295	0.486
	Factor 2 MCP-1 IL-6	−0.196	−0.402	0.029	0.070
	Factor 3 D-Dimer CRP	0.181	−0.045	0.389	0.096
Affectionate Support	Factor 1 uPAR sCD14 sTNFR-II	−0.172	−0.382	0.054	0.112
	Factor 2 MCP-1 IL-6	−0.256	−0.454	−0.034	0.017
	Factor 3 D-Dimer CRP	0.080	−0.147	0.298	0.467
Positive Social Support	Factor 1 uPAR sCD14 sTNFR-II	−0.176	−0.384	0.051	0.106
	Factor 2 MCP-1 IL-6	**−0.290**	**−0.482**	**−0.070**	**0.007**
	Factor 3 D-Dimer CRP	0.183	−0.043	0.391	0.092
Additional Item	Factor 1 uPAR sCD14 sTNFR-II	−0.157	−0.368	0.070	0.149
	Factor 2 MCP-1 IL-6	**−0.268**	**−0.464**	**−0.047**	**0.013**
	Factor 3 D-Dimer CRP	0.174	−0.052	0.383	0.108
Emotional/Informational	Factor 1 uPAR sCD14 sTNFR-II	0.007	−0.217	0.231	0.949
	Factor 2 MCP-1 IL-6	**−0.302**	**−0.492**	**−0.083**	**0.005**
	Factor 3 D-Dimer CRP	0.079	−0.148	0.298	0.469

Corrected for multiple comparisons, significant if p <= 0.0125. **Bold** indicates significant correlation.