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Elevated Plasma Levels of sCD14 and MCP-1 are associated with HIV Associated Neurocognitive Disorders among Antiretroviral Naïve Individuals in Nigeria

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Abstract

Background: Mononuclear cells play key roles in the pathogenesis of HIV associated neurocognitive disorders (HAND). Limited studies have looked at the association of markers of monocyte activation with HAND in Africa. We examined this association among HIV-1 infected patients in Nigeria.

Method: A total of 190 HIV-infected treatment-naïve participants with immune marker data were included in this cross-sectional study. Plasma levels of soluble CD14 (sCD14), soluble CD163, monocyte chemo-attractant protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-α), and neopterin were measured. Demographically adjusted T scores obtained from a 7-domain neuropsychological test battery were generated and functional status assessed using activities of daily living questionnaire. Participants were classified as unimpaired, having asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND), or HIV associated dementia (HAD) in line with the 'Frascati' criteria.

Results: Thirty-two participants (16.8%) had ANI, 14 (7.4%) had MND, while none had HAD. In multivariable linear regression analyses, adjusting for age, gender, education, CD4 count and viral load, mean levels of sCD14 were higher among those with ANI and MND as compared to the unimpaired (p = 0.033 and 0.023 respectively). Similarly, the mean level of MCP-1 was greater

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among those with HAND as compared to the unimpaired (P= 0.047). There were also trends for higher levels of sCD163 and TNF-α among females with MND in univariable analyses.

Conclusion: Levels of monocyte activation markers correlate with the severity of impairment among individuals with HAND. The mechanisms that underlie these effects and the potential role of gender require further study.

Keywords

HIV-1; Monocyte; Markers; Cognitive; Disorders; Nigeria

INTRODUCTION

The advent of combination antiretroviral therapy (cART) has led to remarkable improvement in survival among HIV infected individuals[1–3]. Similarly, a significant reduction in the incidence of severe forms of HIV associated neurocognitive disorders (HAND) has been observed. However, milder forms of HAND persist with high prevalence[4,5]. Such high-level persistence has been attributed to multiple factors, including sequelae of early insult to the central nervous system (CNS) during acute HIV infection, the so-called legacy effect.[6,7] Also contributing to this is the poor CNS penetrance and/or adverse effects of some antiretroviral medications.[8] In addition, there may be neuropathic effects caused by chronic inflammatory response to persisting viral replication, microbial translocation and co-infections.[9] Furthermore, other comorbid conditions may interact with the aforementioned factors in the pathogenic mechanisms involved.[10]

HIV enters the CNS mainly through trafficking of infected mononuclear cells[11]. This leads to a cascade of inflammatory events that result in neural damage.[12] Persistent immune activation especially involving the monocyte-macrophage system has been shown to correlate with the severity of HAND.[7] Elevated plasma levels of soluble CD14 (sCD14), soluble CD163 (sCD163), monocyte chemoattractant protein 1 (MCP-1), and neopterin were found to be associated with HAND[13–16], though only sCD163 appears to show this association among individuals that are virally suppressed[17]. While the specific mechanisms for HAND pathogenesis remain to be fully elucidated, the apparent role of monocyte activation has provided valuable leads for further research towards identifying specific biomarkers and interventions that may address diagnostic and therapeutic needs.

Limited studies have explored the association between markers of monocyte activation and HAND in Africa[18,19]. Thus, it is important to determine whether the association observed in other settings could be replicated in an African setting with different HIV burden, HIV subtypes, comorbidity profile, as well as potentially different background levels of immune activation from prevalent infections and infestations. We earlier reported preliminary findings showing correlations between levels of sCD14 and sCD163 with global impairment among our cohort in Nigeria.[18] In this report, we further examined these and other markers to determine associations with levels of neurocognitive impairment in line with the HAND nosology.

METHODS

Design:

This was a cross-sectional analysis of baseline data from participants in a prospective cohort study of HAND conducted in Abuja Nigeria between 2011 and 2014.

Study Participants:

Participants were enrolled consecutively between 2011 and 2013 from HIV counseling and testing centers at two tertiary facilities, the National Hospital (NHA) and the University of Abuja Teaching Hospital (UATH), both in Abuja, Nigeria. Archived baseline samples from 190 HIV-infected and 70 HIV-uninfected participants were available for the measurement of plasma immune markers. All individuals were ≥18 years of age, able to communicate in English, antiretroviral treatment naïve, and had no history of active tuberculosis, syphilis or other infections. The participants also had no evidence of clinical conditions that could impair their ability to participate in the testing, including active central nervous system (CNS) or systemic disease, history of significant head trauma, current or history of alcohol abuse, use of other mind-altering substances, or evidence of substance use on urine toxicology screening. There was also no previous diagnosis of a learning disability, psychiatric disorder, or other disorders associated with focal neurological deficits. Demographic and clinical information were obtained using standardized questionnaires, including a thorough general medical assessment as well as a comprehensive neuropsychological testing. Informed consent was obtained from all participants and study procedures were approved by the University of Maryland Baltimore, NHA, and UATH Institutional Review Boards.

Neuropsychological assessment

A standardized 22 test neuropsychological battery was administered to all study participants by an examiner blinded to the HIV serological status of the participant. Details of these are described in our other reports.[20–22] Participants were screened for effort using the Hiscock Digit Memory Test, and for depression with the Beck Depression Inventory.[23]

Raw scores from the neuropsychological tests were converted to scaled scores and these were used to generate standardized T-scores adjusted for age, gender and education (with mean of 50 and standard deviation [SD] of 10). Summary domain scores were calculated by averaging test scores for individual tests within each domain. Functional status was assessed using activities of daily living questionnaire. Individuals requiring assistance in at least 2 instrumental activities of daily living (IADL) were considered functionally impaired. Participants were classified as unimpaired, having asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) or HIV associated dementia (HAD), in line with the ‘Frascati’ criteria[24]. Briefly, individuals with neuropsychological test scores at least 1 SD below the normative mean in two or more cognitive domains without evidence of functional impairment were considered to have ANI, while those with functional impairment had MND. Neuropsychological scores at least 2 SDs below the normative mean in two cognitive domains with marked impairment of daily function would fulfill the requirement

for HAD classification. Participants were considered unimpaired if their neuropsychological scores were less than 1 SD below the mean or if only one cognitive domain was affected.

Laboratory Procedures

Participants' blood samples were analyzed for the determination of HIV-1 serological status, measurement of viral load (limit of detection: 20 copies/ml) and CD4+ T cell count as detailed in our other reports.[25] These were performed at the Institute of Human Virology, Nigeria-supported Training Laboratory located in Asokoro, Abuja. Peripheral blood samples were collected in citrate tubes and cells separated from plasma on Ficoll gradients. Aliquots of plasma were stored at −20 degrees until analyzed.

Commercially available kits were used to measure plasma levels of soluble CD14 (sCD14; R&D Systems), soluble CD163 (sCD163; Trillium Diagnostics), neopterin (R&D Systems), monocyte chemo-attractant protein-1 (MCP-1; Luminex Multianalyte System), and tumor necrosis factor-alpha (TNF-α; Luminex Multianalyte System) according to manufacturers' directions.

Statistical Analysis

Demographic and clinical characteristics were compared between HAND categories using chi-square and Kruskal Wallis tests. Univariable and multivariable linear regression models were fit to estimate mean differences between the HAND categories and the unimpaired while adjusting for potential confounding variables (age, gender, education, CD4 count and viral load). A dichotomous variable (HAND versus unimpaired) was also created. With no participants fulfilling the criteria for HAD in this cohort, individuals with ANI or MND constituted the HAND group for our impaired vs unimpaired analysis. The association between HAND and marker levels was further explored using multivariable logistic regression analysis adjusting for same variables as above. Interaction terms between gender and HAND categories were explored, and where significant or showing trends, stratified analyses for males and females were undertaken. Immune marker levels and viral load measurements were log transformed to achieve normality. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc.).

RESULTS

Demographic and Immuno-virologic Characteristics

Among the 190 participants with immune marker test results in this cohort, about 24% had evidence of neurocognitive impairment. Thirty-two participants (16.8%) and 14 (7.4%) had asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) respectively (Table 1). No participant fulfilled the criteria for HIV associated dementia (HAD). Around two-thirds of the participants were females, and those with HAND had even greater proportion of females compared to the unimpaired [P = 0.035]. The median number of years of education was 12 years and this did not differ by HAND category. The median CD4 count was 325 cells /mm^3, while median viral load was 4.5 $\log_{10}$ copies /ml, and both did not differ statistically by HAND classification.

Association between Immune Marker Levels and HAND Categories by Linear Regression Analyses

Soluble CD14: The mean level of sCD14 was significantly higher among HIV-infected when compared to uninfected controls (P < 0.001). Among the HIV infected participants, those with HAND (ANI and MND) also had significantly higher mean sCD14 compared to the unimpaired (P = 0.006) [Figure 1].

In a multivariable linear regression adjusting for age, gender, years of education, CD4 count and viral load, participants with ANI or MND had significantly higher levels of sCD14 than the cognitively unimpaired (Mean difference (MD): 0.17 and 0.21 $\log_e$ pg/ml respectively; P = 0.033 and 0.023 respectively) [Table 2].

Soluble CD163: The mean level of sCD163 was also significantly higher among HIV infected participants as compared to the uninfected (P < 0.001). The mean level among those with HAND (ANI and MND) appeared higher than in the unimpaired but the difference was not statistically significant (P = 0.281) [Figure 1].

The mean levels of sCD163 did not differ statistically between participants with ANI or MND and the unimpaired in both univariable and multivariable regression analyses (MD: 0.04 and 0.18 $\log_e$ ng/ml respectively; P = 0.8 and 0.357 respectively for the multivariable analyses). Among females, there was a trend for higher mean level in those with MND as compared to the unimpaired in univariable analysis (MD: 0.43 $\log_e$ ng/ml; P = 0.079) [Table 2].

MCP-1: The mean level of MCP-1 was significantly greater among those with HAND as compared to the unimpaired (MD: 0.21 $\log_e$ ng/ml; P = 0.047) [Figure 1]. There was also a trend for higher mean level among those with MND as compared to the unimpaired in univariable analysis (MD: 0.26 $\log_e$ ng/ml; P = 0.094) [Table 2].

TNF-α: There was no statistically significant difference in TNF-α mean level between those with ANI or MND and the unimpaired in both univariable and multivariable analyses. However, among females there was a trend for higher mean levels among those with MND when compared to the unimpaired in univariable analysis (MD: 0.33 $\log_e$ ng/ml; P = 0.077) [Table 2].

Neopterin: There was a trend for higher mean level of neopterin among individuals with MND as compared to the unimpaired in both univariable and multivariable analyses (MD: 0.22 $\log_e$ nmol/L; P = 0.054) [Table 2].

Association between HAND and Immune Marker Levels by Logistic Regression Analyses

In a multivariable logistic regression adjusting for age, gender, education, CD4 count and viral load, the odds of neurocognitive impairment were 6.4 times higher per log increase in sCD14 (OR: 6.4 [95% CI: 1.6, 27]; P = 0.011). The association of HAND with sCD163 tended to show similar pattern but not statistically significant (OR: 1.2 [95% CI: 0.7, 2.2]; P = 0.512). The odds of impairment were 2.2 times higher per log increase in MCP-1 (OR: 2.2 [95% CI: 1.03, 4.8]; P = 0.041), after adjusting for the same variables. A similar trend was

observed for neopterin, but this did not reach statistical significance (OR: 1.8 [95%: 0.6, 5]; P = 0.284). For TNF-α, the association tended towards showing lower odds of impairment per log increase that was also not statistically significant (OR: 0.8 [95% CI: 0.4, 1.7]; P = 0.529) [Table 3].

DISCUSSION

In this study, we found significant associations between markers of monocyte activation in plasma and HAND among antiretroviral treatment-naïve patients. Levels of sCD14 and MCP-1 were specifically found to be higher among individuals with neurocognitive impairment as compared to the unimpaired, with some evidence of a hierarchical pattern for the HAND categories.

These results are consistent with reports from other studies. In a cohort comprising predominantly treatment-experienced patients, Ancuta et al.[14] reported significantly higher levels of sCD14 and MCP-1 among individuals with either HIV associated dementia (HAD), or any form of cognitive impairment, when compared to those that were unimpaired. Furthermore, Ryan et al.[26], in a relatively small sample of treatment-experienced patients, found higher levels of sCD14 among individuals with impairment in any cognitive domain when compared to those that were cognitively intact. Similarly, Lyons et al.[13] reported significant association between levels of sCD14 and global neurocognitive impairment, and this appeared to be driven mainly by associations observed within attention and learning cognitive ability domains.

Unlike the latter 2 studies, our study like that of Ancuta et al.[14], with considerably greater power, found significant association for both sCD14 and MCP-1 levels with HAND utilizing ‘Frascati’ and AAN (American Academy of Neurology) definitional criteria[24] respectively, thereby extending and consolidating the earlier findings. Additionally, Marcotte et al.[27], in a longitudinal study, identified a combination of cerebrospinal fluid (CSF) and plasma levels of sCD14 and MCP-1 as the most consistent markers associated with neurocognitive change in prognostic and diagnostic models. A number of other studies have shown similar associations for these and other markers of innate immune activation measured in the CSF[28–32].

This study looked at antiretroviral naïve individuals prior to the current era of universal ‘test and start’ treatment strategy.[33] It differs from similar studies that looked at predominantly treatment experienced participants.[14,26,27] Our findings demonstrate the correlation of monocyte activation markers with cognitive function beyond associations with HIV infection and level of viremia. Therefore, the study provides a complement to the full disease spectrum (early/late and untreated/treated), indicating that the association exists across the entire HIV clinical profile.

The analyses in this study did not find statistically significant associations between levels of sCD163 and TNF-α with HAND, although the level of sCD163 was significantly higher among HIV-infected as compared to uninfected individuals (TNF-α was not measured among the uninfected participants). Interestingly, we did find evidence of trends for higher

levels of these markers among females with MND when compared to their unimpaired counterparts in univariate analyses. This may be suggestive of a potential interaction between gender and these markers in their association with HAND. We previously reported marginal evidence of a weak correlation between global deficit scores (GDS) and sCD163 levels among our study participants, in addition to a moderate correlation for sCD14 among women[18], also suggesting a likely modifying role of gender for immune marker effects on cognitive function. The mechanisms that underlie these effects and the specific role of gender require further study.

The failure to observe strong associations for sCD163 and TNF-α in this study may be related to differences in demographics, clinical phenotype and treatment history between our study participants and those of other studies showing significant associations.[17,27,34] Unlike the other studies where study subjects included those with dementia, our participants had mild to moderate neurocognitive impairment and were all antiretroviral treatment-naïve. It is possible these markers are insufficiently expressed in plasma to distinguish milder forms of HAND, and CSF may provide better distinction in such situations. This is supported by the fact that the preponderance of evidence for these associations comes from studies that looked at central markers.[16,28,35,36] Our study also differs by having relatively younger participants that are predominantly female and without significant history of substance use or hepatitis C virus (HCV) coinfection. Age, gender, substance use and HCV coinfection are known to be associated with innate immune activation, and may interact with HIV infection to potentiate or attenuate the anticipated primary associations.[18,37–40]

Overall, our findings provide additional evidence in support of the important role of the cells of the monocyte-macrophage lineage in the pathogenesis of HAND. Beyond their involvement in viral trafficking to the CNS[11], they are the only cells demonstrated to support chronic productive infection within the CNS compartment[41], in addition to constituting a durable viral reservoir.[42,43] Moreover, infiltration of the CNS by these cells is considered a cardinal feature of AIDS neuropathology, showing significant correlation with HAD.[44,45]

MCP-1 is a potent inducer of monocyte chemotaxis and transmigration across the blood brain barrier (BBB)[46]. It facilitates entry of infected mononuclear cells into the CNS and subsequent infection of resident perivascular macrophages, microglia and to a limited extent astrocytes, in addition to continued activation of these cells[47].

Soluble CD14 is released mainly from membrane surfaces and intracellular pools of monocytes and macrophages, but to a lesser extent also from neutrophils, following activation[48]. Levels of sCD14 have been shown to correlate with levels of other markers of activation like TNF-α, soluble TNF receptors (sTNFR) and bacterial lipopolysaccharides (LPS).[14,26,49] There is also a significant correlation with viral replication and HIV disease progression, in addition to an observed predictive potential for survival.[50] In-vitro studies have demonstrated an enhanced immune response to LPS following addition of sCD14, including from cells lacking CD14 receptors.[51] There are also reports indicating activation of monocytes by sCD14 independent of LPS.[52] While the direct role of sCD14 in HIV-1 pathogenesis remains unknown, its ability to mediate interactions between immune cells and

microbial components suggests a likely immuno-modulatory activity beyond its potential role as a biomarker.[53]

Chronic innate immune activation in HIV patients results primarily from the persisting presence of the virus and its products, but also from other sources of immune activation. The latter includes coinfections, microbial translocation through a leaky gut, and other inflammatory conditions.[54] Overall, systemic immune activation, irrespective of source, has been linked to increased risk for HIV-1 infection, higher viral replication, and disease progression.[18,55] The degree of immune activation among patients in developing settings like Nigeria was reported to be greater than among patients from resource-rich settings where virtually all the earlier studies on immune markers were conducted.[56,57] Higher level of immune activation in resource-limited settings was attributed to the significantly higher burden of microbial infections, including mycobacterial infections (active and latent), malaria and other parasitic infestations known to be potent inducers of innate immune activation.[55,58–60]

Our findings, reproducing those of other studies from resource-rich settings with lower burden of infectious diseases, indicate the strength and universal relevance of the observed association. The expected high level of background immune activation in our study setting may potentially have either a confounding or a synergistic effect on the anticipated relationship between immune markers and cognitive function. The latter appears more likely based on our results, suggesting a likelihood of positive interaction between multiple sources of immune activation to promote HIV disease progression, including downstream complications like HAND. This may be consistent with the proposed ‘multi-hit’ hypothesis of HAND pathogenesis.[61] Studies looking at independent and interactive effects of different sources of immune activation in HAND pathogenesis will be helpful towards elucidating specific mechanisms involved and their significance.

This study has some limitations. The cross-sectional design hampered our ability to establish a clear temporal sequence between the putative predictor and outcome, in addition to the inability to assess longitudinal changes in the pattern of association. Nonetheless, the findings provide additional evidence in support of earlier reports from cross-sectional and longitudinal studies. Other limitations include the lack of participants with severe form of HAND, HAD, and the relative paucity of men in the study, which might account for the failure to observe statistically significant associations for some of the markers explored. In addition, averaging T scores across individual tests to generate domain score might have underestimated the level of impairment compared to the clinical rating approach. However, we found excellent concordance for neurocognitive impairment between our means approach and the global deficit score method in this cohort (Kappa 0.77). Notable strengths of this study include its substantial sample size, with considerably greater power than many earlier studies that explored these associations, in addition to a study population from a setting with high burden of HIV and background immune activation.

Conclusion

In this study, we found significantly higher plasma levels of sCD14 and MCP-1 among individuals with mild to moderate degree of HAND when compared to those that were

unimpaired, in a cohort of antiretroviral treatment naïve participants in Nigeria. This replicates findings of studies from other settings and adds to the body of evidence on the valuable role of the monocyte-macrophage system in the pathogenesis of HAND. Further studies are required to explore diagnostic and prognostic applications of these markers, in addition to the search for therapeutic and preventative interventions.

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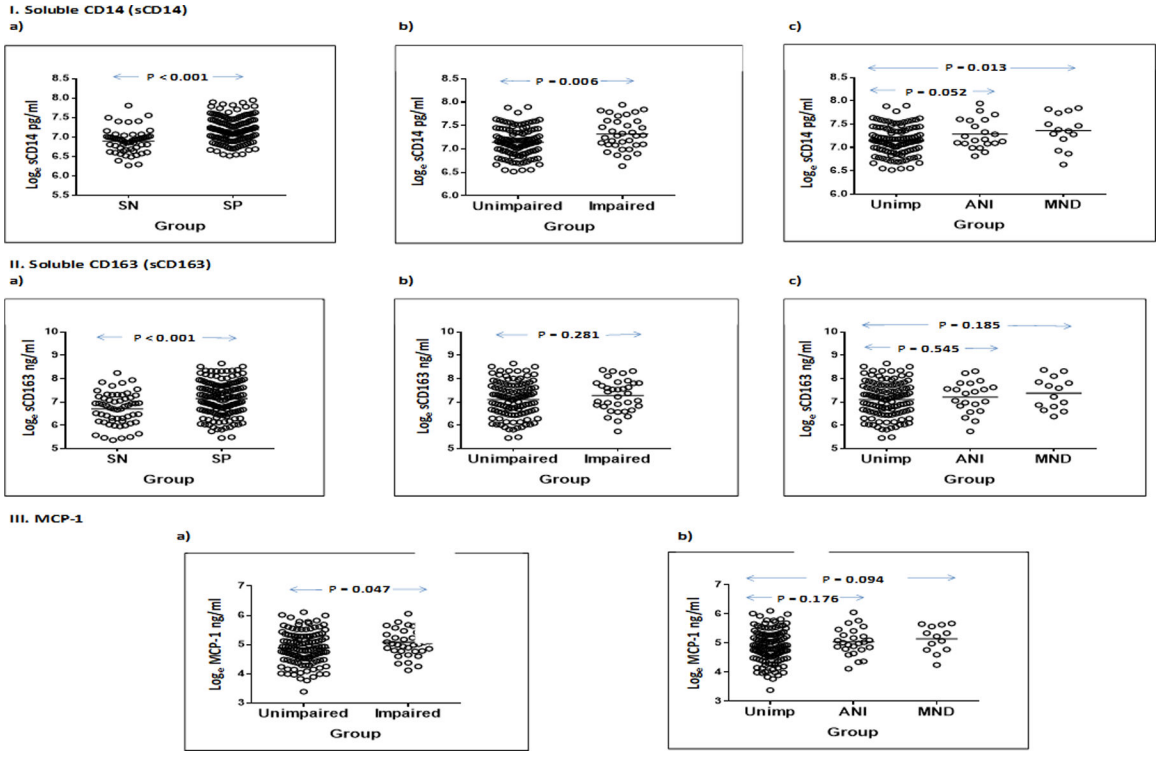

FIGURE 1.

Comparison of Plasma Immune Marker levels by HIV Status and HAND Category.

SN: HIV Seronegative; SP: HIV Seropositive; Unimp: Unimpaired; ANI: Asymptomatic Neurocognitive Impairment; MND: Mild Neurocognitive Disorder; P: P-value (t test); sCD14: soluble CD14; sCD163: soluble CD163; MCP-1: monocyte chemo-attractant protein-1

Table 1:

Demographic and Immuno-virologic characteristics

		All	Unimpaired	ANI	MND	P
	N	190	144	32	14	
Age (years), Median (Q1, Q3)	190	33 (29, 40)	33.5 (29.5, 40.5)	33.5 (28.0, 36.5)	32 (26, 41)	0.557 *
Gender, Female n (%)	124	124 (65.3)	88 (61.1)	26 (81.3)	10 (71.4)	0.083 ^
Education (years), Median (Q1, Q3)	190	12 (12, 15)	12 (12, 14)	12.5 (12, 15)	13.5 (12, 16)	0.114 *
CD4 count cells/μL, Median (Q1, Q3)	182	325 (205, 454)	324 (210, 440)	396 (197, 518)	275 (121, 354)	0.408 *
CD4 Count <200 cells/μL, n (%)	182	43 (23.6)	30 (21.6)	8 (27.6)	5 (35.7)	0.392 ^
Log_{10}Viral Load copies/mL, Median (Q1, Q3)	173	4.5 (4.0, 5.0)	4.5 (3.9, 5.0)	4.4 (3.7, 5.1)	4.9 (4.5, 5.1)	0.220 *
Beck's Depression Score, Median (Q1, Q3)	190	5 (1, 10)	4 (1, 10)	7 (1, 13.5)	7.5 (4, 14)	0.499 *

* Kruskal Wallis

^ Chi square

ANI: Asymptomatic neurocognitive impairment

MND: Mild neurocognitive disorder

N: number of participants

Q1: 25th percentile

Q3: 75th percentile

P: P-value

Table 2:

Univariable and Multivariable Linear Regression for the Association between Immune Marker Levels and HAND

Immune Marker	N	n	HAND Category	Univariable		*Multivariable	
				MD	P	MD	P
sCD14	149	114	Unimpaired	Ref		Ref	
		21	ANI	0.14	0.052	0.17	0.033
		14	MND	0.22	0.013	0.21	0.023
sCD163	149	114	Unimpaired	Ref		Ref	
		21	ANI	0.1	0.545	0.04	0.8
		14	MND	0.27	0.185	0.18	0.357
MCP-1	158	120	Unimpaired	Ref		Ref	
		25	ANI	0.16	0.176	0.19	0.12
		13	MND	0.26	0.094	0.26	0.103
TNF-α	150	112	Unimpaired	Ref		Ref	
		25	ANI	−0.19	0.133	−0.17	0.187
		13	MND	0.23	0.177	0.15	0.373
Neopterin	176	136	Unimpaired	Ref		Ref	
		27	ANI	0.14	0.871	0.0004	0.993
		13	MND	0.22	0.068	0.22	0.054

*Adjusted for age, gender, years of education, CD4 count and viral load,

N: number of participants

MD: Mean Difference

P: P-value

HAND: HIV associated neurocognitive disorders

ANI: Asymptomatic neurocognitive impairment

MND: Mild neurocognitive disorder

Table 3:

*Multivariable Logistic Regression for the Association between HAND and Immune Marker Levels

Marker	N	OR	95% CI	P
Log_eCD14	**149**	6.4	1.6, 27	0.011
Log_eCD163	**149**	1.2	0.7, 2.2	0.512
Log_eMCP	**158**	2.2	1.03, 4.8	0.041
Log_eTNF-α	**150**	0.8	0.4, 1.7	0.529
Log_eNeopterin	**176**	1.8	0.6, 5	0.284

*Adjusted for age, gender, education, CD4, Viral load

N: number of participants

OR: Odds ratio

CI: confidence interval

P: P-value