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Monocyte Activation, HIV and Cognitive Performance in East Africa

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Abstract

Chronic inflammation associated with monocyte activation has been linked to HIV-related cognitive outcomes in resource-rich settings. Few studies have investigated this relationship in the African context where endemic non-HIV infections may modulate effects. We characterized immune activation biomarkers in Kenyan and Ugandan participants in relation to neuropsychological testing performance (NTP) from the African Cohort Study (AFRICOS). We focused on activation markers associated with monocytes (sCD14, sCD163, neopterin), T-cells (HLA-DR$^+$CD38$^+$ on CD4$^+$ and CD8$^+$ T lymphocytes), and microbial translocation (intestinal fatty acid-binding protein, I-FABP). The HIV-infected (n=290) vs. HIV-uninfected (n=104) groups were similar in age with mean (SD) of 41 (9.5) vs. 39 (9.9) years, respectively (p=0.072). Among HIV-infected participants, the mean (SD) current CD4$^+$ count was 402 (232); 217 (75%) were on

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combination antiretroviral therapy (cART) and 199 (69%) had suppressed plasma HIV RNA. sCD14 was inversely correlated to NTP (r=−0.14, p=0.037) in models that included both HIV-infected and uninfected individuals, adjusted for HIV status and research site, whereas sCD163 was not (r=0.041, p= 0.938). Neither of the T-cell activation markers correlated with NTP. In the HIV-infected group, I-FABP was inversely associated with NTP (r=−0.147, p=0.049), even among those with suppressed plasma virus (r=−0.0004, p=0.025). Among the full group, HIV status did not appear to modulate the effects observed. In this cohort from East Africa, sCD14, but not sCD163, is associated with cognitive performance regardless of HIV status. Findings among both HIV-infected and HIV-uninfected groups is supportive that HIV and non-HIV-related inflammatory sources contribute to cognitive performance in this setting.

Keywords

sCD14; Intestinal Fatty Acid-Binding Protein; Eastern Africa; HIV; Cognition Disorders; sCD163

INTRODUCTION

Cognitive impairment impacts up to 50% of people living with HIV (PLWH) in resource-rich settings (Heaton et al, 2011). The estimated prevalence may be lower in Africa as reported in Zambia (33%) (Robertson et al, 2010), Uganda (31%) (Wong et al, 2007), and Botswana (37%) (Lawler et al, 2011), although methodological challenges make it difficult to provide firm estimates. Nevertheless, these studies confirm the presence of HIV-associated cognitive impairment in Africa, a low-resource setting, where little is known about potential determinants of neuropathogenesis.

Non-HIV sources of inflammation are of interest because population-based reports link geographical burden of infectious disease to intelligence quotient (IQ), a measure of cognitive capacity (Eppig et al, 2010; Nakku et al, 2013). This raises the possibility that, in a setting such as the African continent, both HIV and non-HIV-associated immune activation pathways contribute to cognitive impairment in PLWH. Published reports focused on HIV-specific pathways describe links to the virus itself and viral particles as well as chronic immune activation playing active and overlapping roles (Rao et al, 2014).

Two potential immune activation pathways among PLWH include tissue and intra-cellular levels of HIV DNA (e.g. monocytes, lymph nodes, the brain) and gut microbial translocation (Jiang et al, 2009; Brenchley et al, 2006). It is theorized that HIV-activated monocytes cross the blood brain barrier (BBB) and release cytokines and chemokines in the brain parenchyma, which may be directly or indirectly neurotoxic (Persidsky et al, 1999). Viral proteins gp120, Tat, Vpr, and Nef have also been demonstrated *in vitro* to directly damage neurons (Vesce et al, 1997; Pu et al, 2003; van Marle et al, 2009). Additionally, infected astrocytes can damage the BBB, allowing more pro- inflammatory cells and molecules into the brain (Eugenin et al, 2011). Chronic immune activation from gut microbial translocation may further perpetuate systemic and neuroinflammation, affecting cognitive reserve and contributing to cognitive dysfunction (Anuta et al, 2008).

Two monocyte activation markers associated with cognitive impairment in PLWH in resource-rich settings are soluble CD163 (sCD163) and soluble CD14 (sCD14) (Imp et al, 2017). sCD163 is a monocyte-associated hemoglobin-haptoglobin complex scavenger receptor cleaved from activated monocytes (Moller, 2012). In resource-rich settings, plasma sCD163 is higher in PLWH compared to HIV-uninfected people, even with effective cART, and levels are inversely linked to cognitive performance (Burdo et al, 2011; Alcaide et al, 2013; Burdo et al, 2013). In Africa, plasma sCD163 is a risk factor for poor outcomes in HIV-infected individuals starting cART (Scriven et al, 2015; Bestawros et al, 2015) and is inversely linked to cognitive performance (Lyons et al, 2011). sCD14 is a marker of monocyte activation linked to gut microbial translocation as it is derived from a monocyte lipopolysaccharide receptor that is cleaved and released as sCD14. (Triantafilou and Triantafilou, 2002) Higher levels of plasma sCD14 have been associated with cognitive impairment in PLWH (Anuta et al, 2008). The relationship of sCD14 and cognition studied in the African context is limited, but one study of HIV-infected Nigerian women found correlation between higher sCD14 levels and cognitive impairment (Royal et al, 2016). Neopterin is a third marker of monocyte activation; it is a biochemical product of the guanosine triphosphate pathway (Fuchs et al, 1988). Studies have demonstrated a higher expression in HIV-infected compared to HIV-uninfected individuals, also linked to cognitive dysfunction (Fuchs et al, 1989; Griffin et al, 1991). Finally, intestinal fatty acid-binding protein (I-FABP) is expressed in the epithelial cells of the mucosal layer of intestinal tissue. I-FABP is released into the circulation following intestinal mucosal injury, therefore, its plasma concentration has been associated with enterocyte damage and gut microbial translocation. (Lau E et al, 2016).

In this study, we investigated the association of cognitive performance and immune activation in HIV-infected and HIV-uninfected adults in a setting expected to have added endemic infectious vulnerabilities compared to resource-rich areas. We hypothesized that monocyte-associated inflammatory markers would be associated with worse cognitive performance.

MATERIALS AND METHODS

Study design

AFRICOS is a prospective cohort study enrolling HIV-infected (n=3000) and HIV-uninfected (n=600) adults at US Military HIV Research Program (MHRP) President's Emergency Plan for AIDS Relief (PEPFAR)-associated clinical sites in rural Kenya, Tanzania, Uganda, and Nigeria. Inclusion criteria among PLWH were known HIV infection, age 18 years or older, signed informed consent, intent of long-term residency in the area, HIV care recipient, and ability to provide contact information. Exclusion criteria included any significant condition that, in the opinion of the investigators, would interfere with study conduct. The same inclusion and exclusion criteria were applied to HIV-uninfected participants but were required to consent to HIV testing and pre- and post-test counseling. Participants undergo neuropsychological testing at enrollment and every twelve months thereafter. For this analysis, we evaluated the first enrolled participants from the Kenya South Rift Valley (n=304) and Uganda (n=100) sites, chosen considering their geographical

proximity. All participants from these sites who completed neuropsychological testing at baseline and had concurrent inflammatory markers measured were analyzed. All participants consented by institutional review boards approved consent forms.

Clinical Characterization

AFRICOS visits involve comprehensive medical and socio-demographic evaluations with self-reported level of education. The neuropsychological testing battery includes the WHO Auditory Learning Visual Test (WHO AVLT) to test attention (AVLT trial 1), learning efficiency (AVLT sum of trials 1–5), and memory (AVLT recall), Trail Making Test Part A (psychomotor speed), Action Fluency (fluency), and the Grooved Pegboard (manual dexterity) (Maj et al, 1991; Reitan and Wolfson, 1985; Matthews and Klove, 1964). Testers were trained on all neuropsychological tests, certified, and re-certified every 6 months to assure consistent testing across all sites. Individual z-scores were calculated based on normative data collected at the same sites (Milanini et al, 2018). A composite global score was then derived by averaging the individual z-scores (NPZ-6). Assessments of $CD4^+$ T-lymphocyte count and plasma HIV RNA were performed either at CAP-certified MHRP research laboratories or at PEPFAR site clinic labs. Co-infections were defined by concurrent laboratory measures, including a positive hepatitis B surface antigen ELISA, hepatitis C antibody, positive malaria smear, sputum Xpert MTB/RIF, QuantiFERON interferon gamma release essay (performed if ART-naïve), serum cryptococcus antigen positivity (performed if $CD4^+$ count <200 cells/mm^3), and elevated titer for serum Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) for syphilis.

Quantification of Immune Activation

Peripheral blood from participants was processed and reserved for plasma, serum, and peripheral blood mononuclear cells analysis. Soluble factors were measured independently at each site using commercial enzyme-linked immunosorbent assay (EIA) kits or multiplexed assays as per manufacturer's instructions. Levels of sCD14 and sCD163 were measured by Quantikine ELISA (R&D Systems, Minneapolis, MN) and the R&D systems human I-FABP Duo Set EIA kit was used to measure levels of I-FABP. T-cell activation (percentage of CD4 or CD8 T-cells co-expressing HLA-DR and CD38) was determined using a whole blood lyse no-wash flow cytometry procedure as previously described. Commercial antibodies included CD3 PerCP (SK7), CD4 FITC (SK3), CD8 FITC (SK1), CD38 PE (HB7), and HLA-DR APC (L243) (BD Biosciences, San Jose, CA). Samples were examined on a BD FACSCalibur or FACS Canto II and data analyzed using FlowJo version 9.8 (Treestar, Ashland, OR). Cut offs for CD38 and HLA-DR co-expression were set based on CD Chex Normal control gates. For Ugandan samples, EIAs were used to additionally quantify serum neopterin (Immuno-Biological Laboratories America, Minneapolis, MN).

Statistical Analysis

Initially, variables were summarized overall, by country, and by HIV status. Continuous variables were summarized using means and standard deviations, and categorical variables were summarized by counts and percentages. Comparisons between groups were completed by Student's t-test and chi-squared tests. Multivariable linear regressions in the overall sample were used to examine the relationship between the inflammatory markers of interest

and cognitive performance. Adjusted models controlled for site (Uganda vs. Kenya) and HIV status. Follow-up analyses investigated the association between inflammatory markers and cognitive performance among HIV-infected participants, HIV-infected participants without co-infections (of tuberculosis, hepatitis B, hepatitis C, syphilis, and cryptococcosis), and HIV-infected participants who were virally suppressed (RNA <500 copies/mL). Covariates for all three models included $CD4^+$ T-lymphocyte count and plasma HIV RNA. Analyses were performed on Stata (version 15.1, StataCorp, College Station, TX).

RESULTS

Demographic and Clinical Characteristics

Among 394 participants included, 290 (74%) were HIV-infected (Tables 1 and 2) with site distribution of 72 from Uganda and 218 from Kenya. As a group, the HIV-infected participants averaged 41 years of age (range 19–68), 58% were female, and 91% were literate. They self-reported educational attainment to be low, with 40% having some primary school or less and 34% completing primary school and some with secondary school but not having completed that level. The mean (SD) proximal and nadir $CD4^+$ T-lymphocyte count was 402 (232) and 247 (258) cells/mm^3, respectively. Among HIV-infected, 75% were on cART and 32% were treatment naïve. Differences in sCD14 and I-FABP were noted between the HIV-infected and uninfected groups (Table 3).

The HIV-uninfected participants did not differ in age from the HIV-infected group, at 39 years of age (range 19–69, p=0.072). Sex and education did not differ from the HIV-infected group, with 50% female and 90% literate (p=0.162 and 0.713, respectively). They similarly reported a low level of educational attainment with 42% having some primary school or less, 36% having completed primary school and some secondary school.

Monocyte-associated immune activation and cognitive performance

Higher levels of sCD14 were associated with lower NPZ-6 in an analysis of both HIV-infected and HIV-uninfected groups (r=0.0001, p=0.037). No interaction effect of HIV-status was identified. In separate models examining smaller groups stratified by HIV status, no association was observed. Similarly, in sub-analyses among HIV-infected, no associations were noted among virally suppressed participants (p=0.284) or among participants without co-infections (p=0.228). Plasma sCD163 (p=0.938) and neopterin (p=0.659) were not associated with NPZ-6 in the overall sample or in any of the sub-groups (p=0.963, p=0.835).

Intestinal integrity-associated and T-cell activation markers and cognitive performance

Levels of I-FABP were not associated with NPZ-6 scores in the overall sample (p=0.074) and HIV-status interaction effects were not noted. When we examined for associations in only HIV-infected participants, a marginal effect was noted (r=−0.0004, p=0.049) that was stronger among virally suppressed HIV-infected participants examined alone (r=−0.0004, p=0.025). The frequencies of HLA-DR and CD38 expression on both $CD4^+$ and $CD8^+$ T-lymphocytes were not associated with NPZ-6 in the overall sample (p=0.654, p=0.503) or in any of the sub-groups (p=0.763, p=0.927). No association was observed among HIV-infected participants without co-infections.

DISCUSSION

Among our primary hypotheses, only plasma sCD14 levels were associated with overall cognitive performance in a sample of both HIV-infected and HIV-uninfected participants. Within these models, HIV status did not appear to modulate the effect seen between immune activation and cognition in this cohort from East Africa. In exploratory examinations, plasma I-FABP, a marker of enterocyte damage, was inversely associated with cognitive performance, but only in the HIV-infected group. This effect remained present in those that were virally suppressed. This effect was not seen when examining the group without co-infections. The co-infections we quantified included syphilis, hepatitis B, and hepatitis C. Other gut co-infections are common in Africa, including bacterial pathogens such as *E. coli* spp (including enterotoxigenic type), *Shigella* spp, *Salmonella* spp and *Campylobacter* spp. (40%), followed by parasites (27%) such as *Cryptosporidium* spp, *Cyclospora* spp, *Entamoeba* spp and *Blastocystis hominis* and then viruses (22%), mainly rotavirus and adenovirus. A high prevalence of *Cryptosporidium parvum*, *Cystoisospora belli* and microsporidia is reported in HIV-infected adults from the same region (Fletcher et al, 2011). In contrast to other reports, we did not find associations between sCD163 and cognitive performance. Other exploratory immune activation markers similarly were not associated with cognitive performance, including neopterin and T-cell activation markers.

Considering that HIV did not modulate the correlations seen suggests that contributions from non-HIV-related inflammation, potentially from gut- associated inflammatory changes, may play an important role. Early depletion of mucosal CD4+ T cells, loss of immune homeostasis in the gut, and alteration of the normal gut microbiome composition (dysbiosis) are all phenomenon that have been linked to loss of intestinal integrity and persisting immune activation, even after cART and virologic control (Klatt et al, 2013).

Our finding of I-FABP correlating to worse cognitive performance has not previously been reported and is in contrast with one other study of HIV- infected women in the U.S. where no association was found (Imp et al, 2017). A prior study from Uganda suggested a contradicting trend-level decrease in I-FABP among ART-naïve PLWH, although the difference did not meet statistical significance (p=0.07) (Olwenyi et al, 2015). Because these findings were noted only in group level sub-analyses and since no serostatus interaction effects were noted in our main models, these findings should be interpreted with caution. Higher than expected levels of I-FABP in HIV-uninfected participants were seen and similar to levels seen among HIV-infected individuals samples taken from the U.S. (Sandler et al, 2011) This leads us to consider unique competing sources of immunological and gut changes in Uganda that could impact I-FABP's association to HIV outcomes.

These results differ from findings in resource-rich settings that find associations with sCD14 and sCD163, but not I-FABP, which infer a monocyte-driven process (Imp et al, 2017). This discrepancy displays the importance of population context, especially that of co-infections, when assessing the pathogenesis of cognitive impairment. One could postulate that infections endemic to these regions lead to gut microbial translocation and chronic immune activation. For example, intestinal hookworm infection has been suggested to contribute to

cognitive impairment, but the evidence is limited and conflicting (Bartsch et al, 2016; Hotez et al, 2011; Welch et al, 2017; Taylor-Robinson et al, 2015).

We evaluated participants without co-infections of tuberculosis, hepatitis B, hepatitis C, syphilis, and cryptococcosis noting that the effects seen were no longer present; however, this may be due to smaller sample size limiting power. AFRICOS's study design limited our ability to control for other endemic parasitic and enteric diseases, work that might add depth to these hypotheses. However, the known elevated frequency of gut co-infections in this population (Fletcher et al, 2013; Tumwine et al, 2002) that are likely linked to gut microbial translocation, further strengthens our finding that elevated sCD14 and I-FABP levels but not sCD163 are associated with worse cognitive performance. Since gut microbial translocation exists in the context of HIV infection, (Klatt et al, 2013)we can further surmise that this neuropathogenic mechanism is, at least partially, contributing to cognitive impairment in the context of HIV infection in East Africa.

We recognize several potential limitations to our work. As with other epidemiological studies, AFRICOS includes only a limited neuropsychological testing battery, thus, limiting our understanding of global cognition (Robert- son et al, 2010; Wong et al, 2007; Njamnshi et al, 2008; Oshinaike et al, 2010). The AFRICOS methods also limit our ability to assess endemic bio- logical vulnerabilities, especially parasitic and enteric diseases. This reduces our ability to select for HIV-specific contributions to inflammation. Finally, we cannot determine causality because this study was cross-sectional. Prior studies suggest that inflammation has a role in the progression of cognitive impairment (Gorelick, 2010; Simen et al, 2011). Despite these limitations, our measures were developed and validated in the African context and piloted with minor adaptions to local culture for accurate use, strengthening this work (Milanini et al, 2018). The use of co-enrolled HIV-uninfected controls to examine internally standardized performance is a further strength as we did not rely on external normative data that can add external systematic variability.

In conclusion, higher levels of plasma sCD14 but not sCD163, neopterin, or frequency of HLA-DR+CD38+ on both CD4+ or CD8+ T-lymphocytes are inversely associated with worse cognitive performance in men and women from Uganda and Kenya regardless of HIV status. Higher levels of I-FABP were associated with worse cognitive performance, but only in the HIV- infected group, perhaps due to higher propensity for dysbiosis, which has been described in the setting of HIV infection. Our findings add to prior studies by linking inflammation to cognition in the African context.

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Table 1.

Demographic characteristics for all participants at their initial visit (n=394).

Characteristics	HIV-Uninfected (n=104), (%)	HIV-Infected (n=290), (%)	*p*-value
Sex, female	52 (50)	168 (58)	.162
Age, mean (SD; range)	38.9 (9.9; 19–69)	40.9 (9.5; 19–68)	.072
Education			.713
Some primary school or less	44 (42)	115 (40)	-
Completed primary school and some secondary school	36 (35)	98 (34)	-
Completed secondary school and some post-secondary school	32 (31)	64 (22)	-
Ability to read and write	94 (90)	264 (91)	.767
Employed, by self-report	43 (41)	133 (46)	.411
Current depressive symptoms			.896
CES-D 15–21	54 (52)	143 (50)	-
CES-D ≥22	21 (20)	59 (20)	-
Co-infection			
Hepatitis B (n=100)	6 (6)	16 (6)	.856
Hepatitis C (n=102)	2 (2)	4 (1)	.686
Syphilis (n=103)	7 (7)	29 (10)	.332
HIV disease characteristics[†]			
CD4 count, mean (SD)		402.4 (232)	-
Plasma HIV RNA, mean (SD)		53,107.8 (280,454)	-
Virally suppressed		199 (69)	-
cART-naïve		65 (32)	-
On cART		217 (75)	-

[†]Includes HIV-infected subjects only. “Current” refers to within the past week. CES-D=Center for Epidemiological Studies Depression scale. Hepatitis B=Hepatitis B surface antigen. Hepatitis C=Hepatitis C antibody. Tuberculosis=QuantiFERON or TBXpert Test. Cryptococcus=Serum Cryptococcus antigen. Syphilis=Serum RPR or VDRL. Virally suppressed<500 copies/mL=combination antiretroviral therapy.

Table 2.

Demographic characteristics by country and HIV serostatus (n=394).

	Kenya, n (%)			Uganda, n (%)					
Characteristics	**HIV-Uninfected (n=76)**	**HIV-Infected (n=218)**	***p*-value**	**HIV-Uninfected (n=28)**	**HIV-Infected (n=72)**	***p*-value**	***p*-value Kenya vs Uganda HIV-Uninfected**	***p*-value Kenya vs Uganda HIV-Infected**	***p*-value Kenya vs Uganda Overall**
Sex, female	41 (54)	130 (60)	0.386	11 (39)	38 (53)	0.225	0.185	0.307	0.111
Age, mean (SD)	38.4 (9.8)	41 (9.4)	0.036	40.3 (10.4)	40.4 (9.8)	0.969	0.397	0.623	0.989
Education			0.573			0.208	0.345	<0.001	<0.001
Some primary school or less	29 (38)	69 (32)	0.397	15 (54)	46 (64)	0.369	0.187	<0.001	<0.001
Completed primary school and some secondary school	22 (29)	71 (33)	0.569	10 (36)	24 (33)	0.818	0.212	0.416	0.319
Completed secondary school and some post-secondary school	17 (22)	85 (39)	0.003	1 (4)	1 (1)	--	--	--	--
Ability to read and write	72 (95)	212 (98)	0.198	22 (79)	52 (72)	0.516	0.022	<.0001	<0.001
Employed	16 (21)	6321 (29)	0.177	27 (96)	70 (97)	0.835	<0.001	<0.001	<0.001
Current depressive symptoms			0.817			0.814	<0.001	<0.001	<0.001
CES-D ≤14	13 (17)	43 (20)		16 (57)	44 (61)	--	--	--	--
CES-D 15–21	45 (59)	120 (55)		9 (32)	23 (32)	--	--	--	--
CES-D ≥22	18 (24)	54 (25)		3 (11)	5 (7)	--	--	--	--
Co-infection									
Hepatitis B	5 (7)	6 (3)	0.106	1 (4)	10 (14)	--	--	--	--
Hepatitis C	0 (0)	1 (<1)	--	2 (7)	3 (4)	--	--	--	--
Syphilis	5 (7)	27 (12)	0.171	2 (7)	2 (3)	--	--	--	--
HIV Disease[†]									
CD4 count, mean (SD)		397 (249)	--	--	420 (174)	--	--	0.389	--
Plasma HIV RNA, mean (SD)		65,555 (32,205)	--	--	15,938 (45,312)	--	--	0.029	--
Virally suppressed		146 (68)	--		53 (74)	--	--	0.381	--
cART-naïve		53 (24)	--		12 (17)	--	--	0.196	--
On cART		162 (74)	--		55 (76)	--	--	0.757	--

[†]Includes HIV-infected subjects only. “Current” refers to within the past week. CES-D=Center for Epidemiological Studies Depression scale. Hepatitis B=Hepatitis B surface antigen. Hepatitis C=Hepatitis C antibody. Tuberculosis=QuantiFERON or TBXpert Test. Cryptococcus=Serum Cryptococcus antigen. Syphilis=Serum RPR or VDRL. Virally suppressed<500 copies/mL. cART=combination antiretroviral therapy.

Table 3.

Immune activation markers by HIV serostatus (n=394).

	Overall			HIV-Uninfected			HIV-Infected			*p*-value comparing HIV− and HIV+
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	
sCD14	394	1953	636.5	104	1661	574.1	290	2058	637.0	0.001
sCD163	394	1119	794.4	104	1116	1075.9	290	1120	668.3	0.961
I-FABP	394	2171	2528.3	104	1406	1350.5	290	2447	2784.9	0.003
Neopterin	100	7.4	9.40	28	8.3	13.73	72	7.0	7.15	0.543
$CD4^+$ $HLA\text{-}DR^+CD38^+$	333	4.4	5.65	73	3.9	6.60	260	4.5	5.36	0.395
$CD8^+$ $HLA\text{-}DR^+CD38^+$	333	8.0	9.22	73	6.7	8.67	260	8.4	9.35	0.164

SD=Standard deviation. sCD14=soluble CD14. sCD163=soluble CD163. I-FABP=Intestinal fatty acid-binding protein. T-lymphocyte $CD4^+HLA\text{-}DR^+CD38^+$. T-lymphocyte $CD8^+HLA\text{-}DR^+CD38^+$.