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Asymptomatic Malaria Co-infection of HIV-Infected Adults in Nigeria: Prevalence of and Impact on Cognition, Mood, and Biomarkers of Systemic Inflammation

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Abstract

Background: HIV and malaria are associated with immunological perturbations and neurocognitive disorders even when asymptomatic. However, the effect of asymptomatic malaria (AM) in HIV-infected adults on neurocognitive impairment (NCI) is not well understood. This study investigated the biomarkers of systemic inflammation and neurocognition in dually infected Nigerian adults.

Methods: We assessed the HIV and AM status of 269 adults and measured their global and domain-specific neurocognition and depression using standardized measures. Blood levels of sCD14 and sCD163 were also measured.

Results: The mean age of the participants (n = 269) was 33 years, 62% were women, and AM among HIV+ and HIV− was similar (36% versus 37%). NCI was found in 23% (62/269) of participants. HIV+/AM+ had a higher prevalence of impaired learning and executive functions and were more depressed than HIV−/AM− or HIV+/AM−. HIV+ with $CD4^+$ T-cell counts #200/μL were more impaired in the learning domain than those with .200/μL. HIV+/AM+ group had higher levels of sCD14 compared to the other 3 groups and higher levels of sCD163 than the HIV−/AM− group. Higher levels of sCD14 and sCD163 were each associated with NCI. The sCD163 (log10) levels were higher for those with 1+ versus 2+ parasitemia level.

Conclusions: HIV and AM coinfection was associated with an increased risk of reduced learning and executive functions, and elevated systemic inflammation. Mood was more depressed

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in HIV patients with than those without AM. The mechanisms and long-term effects on neurocognition and depression among HIV+/AM+ individuals should be studied because this coinfection is common globally.

Keywords

asymptomatic malaria; HIV co-infection; HIV-associated neurocognitive disorders; soluble CD14 (sCD14); soluble CD163 (sCD163)

INTRODUCTION

Current antiretroviral therapy (ART) can suppress HIV in blood to very low levels,[1] restore $CD4^+$ T-cell counts, but not completely normalize the health of HIV-infected persons.[2] Some patients who achieve sustained suppression of HIV with ART have chronic systemic inflammation (monocyte/macrophage activation) that is associated with lower life expectancy and impaired neurocognitive functioning.[3–6] Acute and chronic co-infections such as malaria, active tuberculosis, syphilis, and hepatitis B and C may contribute to these and other health problems.[7–11]

In malaria-endemic regions, HIV+ persons are more likely to acquire acute malaria that ranges from mild to severe and is associated with higher HIV RNA levels in blood and faster $CD4^+$ T-cell decline.[12] Asymptomatic malaria (AM), characterized by parasitemia without symptoms of acute malaria, is prevalent at rates up to 60% in regions with high malaria transmission.[13] AM may not be benign, as indicated by impaired cognition and anemia among children with AM.[14] However, the effects of AM on cognition in adults, including those co-infected with HIV, has not been reported.

A possible common mechanistic pathway for NCI in AM and HIV co-infection may be systemic inflammation resulting from monocyte and macrophage activation. In spite of optimal ART, many HIV+ patients have elevated blood biomarker levels of systemic inflammation such as soluble (s) CD14 and soluble (s)CD163.[15] Similarly, elevated sCD163 levels are found in children with either asymptomatic and acute malaria.[16,17] Biomarkers of monocyte/macrophage activation have been linked to worse performance on neuropsychological (NP) assessments for people living with HIV.[18–20] However, the effects of HIV+/AM+ co-infection on monocyte/macrophage activation and cognition have not been studied. Thus, we evaluated the effect of AM on neurocognition and sCD14 and sCD163 levels among HIV-infected and uninfected adults in Abuja, Nigeria.

METHODS

Study Design

This is a cross-sectional analysis of prospectively collected data and stored specimens from an NIH-funded, neuroAIDS study in Abuja, Nigeria. Data were collected between April 2011 and November 2012 and included medical and cognitive assessments and blood biomarkers of systemic inflammation from 269 adults: 174 HIV+ antiretroviral-naïve and 95 HIV− participants.

Subjects

At enrollment, none of the participants had current or recent acute malaria, based on clinical history and physical examination. At the time of study enrollment, the HIV+ group were screened to determine whether they met criteria for ART initiation, using criteria established by the Federal Ministry of Health of Nigeria.[21] Those who were started on ART were not included in our study. Neuropsychological performance (NP) data were obtained and serum or plasma samples collected and stored at −80°C until assayed for biomarkers. The study was approved by the local and US institutional review boards and all the participants provided written informed consent.

NP Assessment

All the participants were tested using the HIV Neurobehavioral Research Program International NP battery that assesses function in the 7 major cognitive domains affected by HIV infection: learning, recall, attention/working memory, speed of information processing, verbal fluency, executive function, and motor ability.[22] The raw test scores were standardized by adjusting for age, education, and sex to generate T-scores that were converted to deficit score ranging from 0 ($T > 39$, normal cognition) to 5 ($T < 20$, severe impairment) and the mean deficit scores for tests within each cognitive domain were used to generate a domain-specific deficit score. The average of the deficit scores for all available tests across the 7 domains was the Global Deficit Score. Neurocognitive impairment (NCI) was defined globally as global deficit score ≥0.5 and for each domain as domain-specific deficit score >0.5. The Beck Depression Inventory was used to assess the frequency and severity of depressive symptoms.

Laboratory Assays

Malaria diagnosis was made by examining Giemsa-stained thick and thin peripheral blood smears under a microscope and quantifying parasitemia using the WHO criteria.[23] We used enzyme-linked immunosorbent assays to measure sCD14 (R&D Systems) and sCD163 (sCD163; Trillium Diagnostics) levels following the manufacturers' protocols. The limit of detection was 62.5 pg/L for sCD14 and <0.23 ng/L for sCD163. Clinical laboratory assays also included complete blood counts, and liver and renal function tests. $CD4^+$ T-cell counts were measured by flow cytometry and HIV viral load was measured using the Roche Amplicor Monitor Test (limit of detection of 20 copies/mL).

Statistical Analysis

Before all testing, assumptions for parametric methods were checked; variable transformations ($\log_{10}$) or alternative nonparametric methods were used when needed. Demographic, clinical, and laboratory values were compared among the 4 groups: (HIV−/AM−, HIV−/AM+, HIV+/AM−, HIV+/AM+), using analysis of variance (or nonparametric Kruskal–Wallis test) for continuous variables, and χ^2 test or Fisher exact test for categorical variables. Significant tests were followed up with pairwise comparisons using *t* test (or Wilcoxon), χ^2 or Fisher exact tests, all with false discovery rate (FDR) correction for multiple testing. Chi-square test or Fisher exact test were also used to compare percents of global and domain impairment between the 4 groups. Alternatively, logistic regression

models were used to regress global and domain impairment on HIV status (HIV− and HIV+) and AM status (AM− and AM+). Interactive effects of HIV and AM status on impairment were investigated but none were statistically significant. Odds ratio (OR) assessed effect size, with values above 1 indicating higher odds of impairment. Similarly, effects of HIV-related covariates were assessed in HIV+ group only. Levels of biomarkers measured were compared among the 4 groups and pairwise comparisons with FDR adjustment were done to ascertain significant differences between groups. All analyses with P values <0.05 were considered statistically significant. Data were analyzed using JMP software version 14.0 or R version 3.6.2.

RESULTS

Demographics and Disease Characteristics

Table 1 lists the demographic and clinical characteristics of the participants by group. Participants were predominantly women (62%) with a mean age of 33 ± 8 years and mean education of 13 ± 3 years. The HIV+ group compared with the HIV2 group was older (34 versus 30 years, $P < 0.01$) and less educated (12 versus 14 years, $P < 0.001$). Moreover, in bivariate comparisons among our 4 HIV± and AM± groups, 4 of 6 comparisons of years of educational attainment were significantly different (H−/M− versus H+/M−: $P < 0.001$; H−/M− versus H+/M+: $P = 0.001$, H−/M+ versus H+/M−: $P = 0.018$, H−/M+ versus H+/M+: $P = 0.028$). Age and education influence expected levels of normal performance on cognitive testing that are required for calculating deficit scores. Having a sizeable HIV−/AM− control group allows us to calculate deficit scores that adjust for these factors based on data from the local population.

Levels of malarial parasitemia in peripheral blood smears ranged from 1+ (83%) to 2+ (17%) using the WHO criteria. ART had not been initiated at time of study in the HIV+ patients. HIV RNA was detectable in 93% and median $CD4^+$ T-cell count was 346 cells/μL.

Contribution of HIV and AM to NCI

Global and domain-specific impairment by HIV and AM status is shown in Table 2. All 4 groups (HIV−/AM−, HIV−/AM+, HIV+/AM−, HIV+/AM+) were compared (6 total comparisons) and the pairwise P-values were adjusted for multiple testing. HIV+/AM+ group compared with the HIV−/AM− group had higher impairment in learning ($P = 0.03$) and executive function domains ($P = 0.01$). The logistic regression analysis showed that HIV infection regardless of AM status was associated with global impairment (OR 2.22, $P = 0.02$) (Table 3). The interaction between HIV and AM on NCI was not statistically significant ($P = 0.9$) (data not shown). A model without the interaction term showed that the effect of HIV on prevalence of impairment remained significant for global and 4 domains. In contrast, the effect on global and domain impairment due to AM regardless of HIV status was not statistically significant (all $P > 0.08$).

Contribution of HIV and AM to Depression

Co-infected participants (HIV+/AM+) had the highest Beck depression scores (Beck Depression Inventory 8.9) and the highest proportion of participants diagnosed as depressed (19%), compared with the other 3 groups (range: 1%–12%).

Association of NCI With CD4+ T-Cell Counts

Among HIV+ participants with $CD4^+$ T-cell counts ≤200 cells/μL, AM+ participants had a higher prevalence of impaired learning than AM− (58% versus 18%, $P = 0.03$). In contrast, those with $CD4^+$ T-cell counts >200 cells/μL did not (19% versus 22%, $P = 0.7$).

Systemic Inflammatory Markers and Their Associations With NCI, CD4, and Viral Load

Blood sCD14 $\log_{10}$ levels were significantly higher in the HIV+ versus HIV− group after controlling for AM status ($P < 0.001$) (Table 1). Likewise, they were higher in the AM+ than AM− group after controlling for HIV (Cohen d = 0.35, 95% CI: 0.07 to 0.63; $P = 0.02$). The level of sCD14 in the HIV+/AM+ group was significantly higher than the other groups (Fig. 1): versus HIV−/AM− (Cohen d = 1.25, 95% CI: 0.71 to 1.80; $P = 0.001$); versus HIV−/AM+ (Cohen d = 1.08, 95% CI: 0.47 to 1.69; P ≤ 0.001); versus HIV+/AM− (Cohen d = 0.41, 95% CI: 0.07 to 0.75; $P = 0.017$).

Significantly higher levels of sCD163 also occurred in the HIV+/AM+ group compared with the HIV−/AM− group (Cohen d = 0.69, 95% CI: 0.14 to 1.23; $P = 0.006$). In all the participants, a unit increase in sCD163 $\log_{10}$ was associated with a five-fold increased odds of developing NCI (OR 5.1, 95% CI: 1.8 to 15.1; $P = 0.002$).

$CD4^+$ T-cell count was associated with sCD14 (log10) negatively and nonlinearly; the Spearman correlation coefficient is 20.37 (P < 0.001). If modeled with a quadratic term, that is, regressing sCD14 (log10) on CD4 + CD4^2 (Fig. 2), the association is significant after controlling for HIV and AM in a linear regression model (F = 3.53, df1 = 2 df2 = 207, $P = 0.031$). The effects of HIV and AM on sCD14 (log10) are also significant. Because HIV and $CD4^+$ T-cell count are correlated, although not enough to cause multicollinearity in the above model, a model with just $CD4^+$ terms and AM was also tested. The association between sCD14 (log10) and $CD4^+$ T-cell count remains significant after controlling for AM (F = 14.68, df1 = 2 df2 = 208, P < 0.001), but the effect of AM on sCD14 (log10) is not significant in this model ($P = 0.07$).

$CD4^+$ T-cell count was associated with sCD163 (log10) negatively and linearly. Simple correlation using the Pearson method finds r = −0.27 ($P < 0.001$). The association is nearly significant after controlling for HIV and AM in linear regression (F = 3.76, df1 = 1 df2 = 206, $P = 0.054$). The effects of HIV and AM on sCD163 (log10) are not significant in this model. After controlling for malaria alone, $CD4^+$ T-cell count and sCD163 (log10) remain significantly correlated (F = 14.8, df1 = 1 df2 = 207, $P < 0.001$). The effect of AM on sCD163 (log10) is not significant in this model ($P = 0.53$).

In HIV+ participants, HIV viral load (log10) and sCD14 (log10) were positively correlated; Pearson r = 0.23 ($P = 0.004$). This association remained significant, after controlling for AM (F = 7.8, df1 = 1 df2 = 146, $P = 0.006$), and the effect of AM was also significant ($P =$

0.03). Similarly, the Pearson correlation for HIV viral load (log10) and sCD163 (log10) was positive and significant (r = 0.23, $P = 0.004$). In a model adjusting for effect of AM, the association between HIV viral load (log10) and sCD163 (log10) was statistically significant ($P = 0.005$), although the AM itself was not associated with sCD163 (log10) in this model ($P = 0.44$).

Association of Malarial Parasitemia Levels With Biomarkers of Systemic Inflammation

In AM+ participants, mean sCD14 (log10) values did not differ between levels of malarial parasitemia (3.12 versus 3.10, $P = 0.56$). The average values of sCD163 (log10) were higher for patients with 1+ level of parasitemia compared to those with 2+ level (3.11 versus 2.85, $P = 0.016$). The difference remained significant after controlling for HIV status ($P = 0.026$), and HIV was also significantly associated with higher sCD163 (log10) level in this model ($P = 0.036$).

DISCUSSION

We estimated the prevalence of asymptomatic malarial parasitemia (AM) among HIV+ and HIV− men and women in Abuja, Nigeria, and investigated its association with impaired cognition (multi-domain neuropsychological assessment), depressed mood (Beck Depression Inventory) and blood biomarkers of systemic inflammation that are linked to monocyte/macrophage activation (sCD14 and sCD163). AM was found in a third of our participants and did not differ by HIV status in this cohort.

This study is the first to examine the combined effect of HIV and AM on global and specific domains of cognition in adults. HIV has been known to damage the brain for more than 4 decades.[24] Optimal ART fails to reverse the resulting cognitive impairment in a substantial fraction of these patients.[25] As expected, our HIV+ participants, all of whom had not yet commenced ART, were impaired compared with HIV− controls in cognitive domains of executive function and learning.[26,27] However, AM alone or in combination with HIV was not associated with impaired global cognition. HIV+/AM+ participants were more impaired in cognitive domains of executive function and learning compared with the HIV−/AM− group.

The HIV+/AM+ group had the highest levels of sCD14 and sCD163, which were associated with increased odds of NCI. The HIV+/AM+ group with $CD4^+$ T-cell counts ≤200 cells/μL were more impaired in the learning domain and higher biomarkers of systemic inflammation than the HIV+/AM− group. Thus, AM may adversely affect cognition in HIV+ persons with worse immunosuppression by enhancing systemic inflammation.

Coinfected patients were also more likely to endorse markers of depressed mood. A possible mechanism for both of these observations is systemic inflammation. Depression has been linked to elevated blood levels of proinflammatory cytokines and chemokines, and other biomarkers such as C-reactive protein, TNFα, IL-6, and MCP-1.[28,29] Systemic inflammation can cause central nervous system inflammation that damages the brain. In our coinfected patients, we hypothesize that a similar mechanism may be playing a role resulting in higher depression.

The prevalence of AM in this study (33%) is slightly lower than the 40% found in another Nigerian study using similar methods of detection.[30] This difference may be attributable to inclusion in that study of children who had a higher prevalence of AM, whereas our study excluded children. Within Abuja, where our study originated, rates of AM differ, depending on where participants live. For example, a study found AM prevalence of 70% among participants, with higher rates in those who live in houses with bushes nearby.[31] A more recent study in a forested region of Nigeria found AM in 57% in contrast to the savanna region of Abuja where this study originated.[31,32] The 2-fold greater prevalence of AM in these studies compared with ours may be attributed to geographical differences in the prevalence of mosquitos and malaria in these regions. Rates from other sub-Saharan countries range from 6.7% to 60.6%; reflecting the variable endemicity and control of malaria based on socio-economic status, cultural norms, and public health practices.[33–35]

Studies in children have found a higher prevalence of AM among HIV+ than HIV− participants.[36] However, AM prevalence in HIV+ adults has not been reported previously. Immunosuppression due to HIV contributes to a higher risk of acute malaria and severe infection.[37,38] Prevalence of AM among HIV+ persons may be affected by immunosuppression in either of 2 directions: increased because HIV infection increases susceptibility to malarial infection or decreased by higher rates of progression from AM to acute malaria. The similar prevalence of AM among HIV+ and HIV− persons in our study may result from a combination of these 2 opposing effects of HIV.

In diseases such as HIV and AM, chronic systemic inflammation reflecting monocyte/macrophage activation may be implicated in pathogenesis of NCI.[26,39–41] HIV+ persons have higher sCD14 and sCD163 levels in blood compared with HIV−.[15] In addition, sCD163 levels were associated with HIV-associated NCI in a recent study of ART-naïve HIV+ persons in Nigeria.[19] Mean levels of sCD14 were higher among those with asymptomatic and mild NCI when compared with the unimpaired ($P = 0.033$ and 0.023 respectively) implying association of NCI with severity of monocyte activation.[42] Similarly, elevated levels of sCD14 and sCD163 have been reported in acute and AM.[43,] The higher sCD14 and sCD163 levels in our co-infected group (HIV+/AM+) indicates an additive effect of both infections on systemic inflammation. These markers were also associated with worse NCI, but no interaction between HIV and AM was found.

We found unexpectedly higher levels of sCD163 in our AM patients with 1+ than with 2+ parasitemia. sCD163 is the soluble form of an anti-inflammatory glycoprotein on macrophages, levels of which rise as a late reaction to inflammatory processes. A study of Cameroonian children with either asymptomatic (AM) or uncomplicated symptomatic falciparum malaria (UM) found that children with AM compared with UM were (1) older (6 versus 3 years) (2) had much lower levels of parasitemia (765 versus 58,300 parasites/μL), (3) lower levels of proinflammatory sCD14 (4200 ng/mL versus 11,700 ng/mL) and (4) similar levels of sCD163 (514 versus 530 ng/mL).[16] They did not examine the relationship of sCD163 to levels of parasitemia within the children with AM. Based on this study and our results, we hypothesize that our adults with AM and 1+, compared with those with 2 +parasitemia, had provoked similar levels of inflammation, but were more effective and elicited higher sCD163 levels.

The effect of AM on cognition in adults has not been previously reported, but, both acute and AM in children has been found to impair cognition. One study found lower abstract reasoning and sustained attention in AM+ children when compared with AM− suggesting an underlying immunological response or pathway.[44]

Major strengths of this study are: (1) assessment of systemic inflammation with several established biomarkers, (2) use of a rigorous, validated neuropsychological test battery, and (3) large fraction of patients and controls with AM and HIV that allows examination of the roles of both infections and their potential interaction.

Main limitations of this study include its cross-sectional design, small number of subjects who were limited to adults, and assessment of systemic inflammation with only 2 biomarkers. AM diagnosis could potentially include 3 different stages of infection: recently infected asymptomatic, presymptomatic, and chronically infected asymptomatic that cannot be determined without longitudinal observation.[45] Because our study was cross-sectional of necessity, we cannot differentiate among these different states. Other limitations include: (1) other regionally prevalent co-infections may contribute to elevated sCD14 and sCD163 levels, but were not assessed; (2) biomarkers in cerebrospinal fluid may better represent neuro-inflammation that affects cognition than those measured in blood, but CSF specimens were not collected, and (3) limited diagnostic sensitivity for diagnosis of AM compared with more sensitive techniques such as PCR.

Future studies are needed to assess such questions as: What are the long-term effects of AM on monocyte/macrophage activation and cognition? Do AM severity, as measured by parasitemia, sCD14 and sCD163 levels, and cognitive impairment vary over time? Do AM effects cumulate leading to progressive decline in cognition? Does AM treatment arrest or reverse the impairment?

SUMMARY AND CONCLUSIONS

In summary, co-infection with AM and HIV in our cohort of urban Nigerian adults was common and associated with an increased risk of impaired executive function and learning, but not global impairment. The HIV and AM co-infected participants also reported the highest frequency and severity of symptoms of depression. Two biomarkers of systemic inflammation, sCD14 and sCD163 were highest in the HIV+/AM+ groups and were associated with NCI. The mechanisms and long-term effects of AM and HIV coinfection on neurocognition should be investigated in larger, longitudinal studies. In such studies, changes in systemic inflammatory biomarkers should be compared with neurocognition before and after treatment for both infections. This information may help to prioritize diagnostic and treatment policies for AM in HIV infection.

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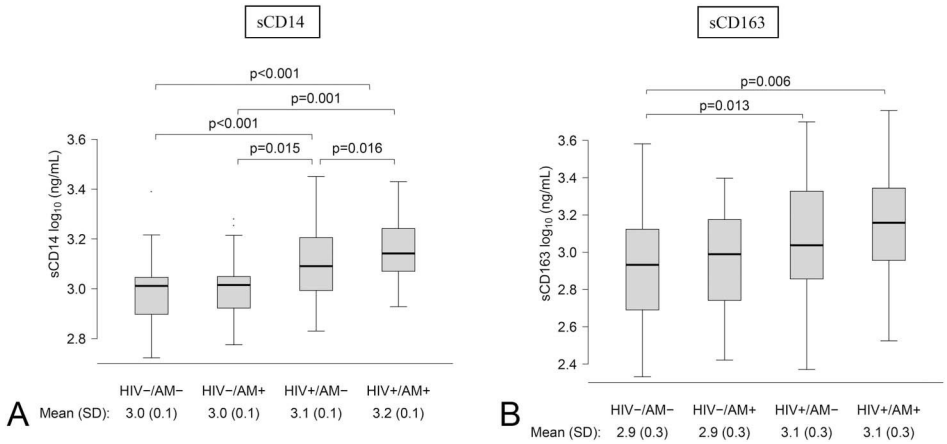

FIGURE 1.

sCD14 and sCD 163 levels by infection with HIV and asymptomatic malaria after adjustment for multiple testing. Levels of inflammatory biomarkers in 4 groups. A, sCD14 levels were significantly higher in the HIV+/AM+ group than the other groups and also higher in the HIV+ versus HIV− and AM+ versus AM− groups after controlling for AM and HIV, respectively. B, sCD163 levels were significantly higher in the HIV+/AM+ versus HIV−/AM− group.

TABLE 1.

Demographic and Clinical Characteristics of Participants

Variable	All Groups (269)	A: HIV−/AM− (67)	B: HIV−/AM+ (28)	C: HIV+/AM− (112)	D: HIV+/AM+ (62)	Significant Differences*
Gender (male)[1]	101 (38%)	22 (33%)	10 (36%)	46 (41%)	23 (37%)	
Age (years)[2]	32.7 (7.6)	29.3 (6.5)	30.6 (7.1)	34.3 (7.6)	34.3 (7.6)	A, B < C, D
Education (years)[2]	12.9 (3.0)	14.1 (2.0)	13.9 (2.4)	12.3 (3.3)	12.3 (3.2)	A, B > C, D
Beck Depression Index[2]	6.5 (6.6)	4.7 (4.7)	5.9 (6.3)	6.3 (6.8)	8.9 (7.6)	A, C < D
Depressed (n, %)[1,4]	28 (10%)	1 (1%)	2 (7%)	13 (12%)	12 (19%)	A < D
Current $CD4^+$ T (cells/μL)[3]	458 (269–706)	749 (569–870)	804 (653–903)	358 (234–518)	297 (190–419)	A, B > C > D
$CD4^+$ T ≤200 (cells/μL)[1]	35 (13%)	0 (0%)	0 (0%)	18 (16%)	17 (28%)	A, B < C, D
HIV RNA viral load (log_{10} copies/mL)[3]	4.6 (3.9–5.1)	—	—	4.5 (3.8–5.0)	4.7 (4.1–5.2)	
HIV RNA >50[1]	141/151 (93%)	—	—	89/95 (94%)	52/56 (93%)	
Hemoglobin (g/dL)[3]	12.4 (11.6–13.5)	12.8 (12.3–13.7)	12.4 (11.8–13.6)	12.1 (11.2–13.5)	12.1 (11.1–13.5)	A > C, D
Global Deficit Score[2]	0.31 (0.30)	0.24 (0.23)	0.22 (0.27)	0.33 (0.29)	0.39 (0.34)	A, B < D
Global Deficit Score ≥ 0.5[1]	62 (23%)	10 (15%)	4 (14%)	32 (27%)	16 (26%)	
sCD14 (log_{10} mg/L)[2]	3.09 (0.15)	2.99 (0.12)	3.01 (0.14)	3.10 (0.14)	3.16 (0.12)	A < C, D; B < D
sCD163 (log_{10} mg/L)[2]	3.05 (0.32)	2.91 (0.31)	2.94 (0.28)	3.08 (0.32)	3.13 (0.29)	A < C, D

1: count (%)

2: mean (SD)

3: median (interquartile range)

4: depressed if Beck Depression Index >15.

*** Adjusted for multiple comparisons by FDR method.

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TABLE 2.

Pairwise Comparison of Prevalence (Number and %) of Global and Domain-Specific Impairment Adjusted for False Discovery Rates in Four Groups

Cognitive Domains	All Participants (269)	A: HIV−/AM− (67)	B: HIV−/AM+ (28)	C: HIV+/AM− (112)	D: HIV+/AM+ (62)	*P*	Significant Differences*
Global	62 (23)	10 (15)	4 (14)	32 (27)	16 (26)	0.12	
Learning	44 (18)	5 (7.5)	3 (11)	20 (18)	16 (26)	0.03	A < D
Recall	49 (18)	11 (16)	2 (7.1)	21 (19)	15 (24)	0.27	
SIP†	61 (26)	10 (15)	4 (14)	30 (27)	17 (27)	0.15	
Motor	64 (24)	15 (22)	3 (11)	26 (23)	20 (32)	0.16	
Executive function	52 (19)	5 (7.5)	4 (14)	25 (22)	18 (29)	0.01	A < D
Working memory	28 (10)	5 (7.5)	6 (21)	10 (8.9)	7 (11)	0.21	
Verbal	67 (25)	13 (19)	5 (18)	28 (25)	21 (34)	0.21	

*Adjusted for multiple comparisons by FDR method.

†SIP, speed of information processing.

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TABLE 3.

Logistic Regression of the Prevalence of Global and Domain-Specific Impairment by HIV and Asymptomatic Malaria

	All HIV+ vs HIV−		All AM+ vs AM−	
NP Impairment	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Global	2.22 (1.2 to 4.3)	0.02	0.89 (0.48 to 1.6)	0.70
Learning	3.32 (1.5 to 8.1)	<0.01	1.53 (0.76 to 3.1)	0.23
Recall	1.98 (1 to 4.12)	0.06	0.98 (0.49 to 1.9)	0.96
SIP	2.76 (1.4 to 5.6)	<0.01	1.02 (0.54 to 1.9)	0.95
Motor	1.05 (0.5 to 2.3)	0.9	0.43 (0.09 to 1.4)	0.21
Executive function	3.25 (1.5 to 7.5)	<0.01	1.81 (0.92 to 3.6)	0.08
Working memory	0.98 (0.44 to 2.3)	0.96	1.87 (0.83 to 4.2)	0.13
Verbal	2.13 (1.2 to 4.1)	0.02	1.37 (0.75 to 2.5)	0.31