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Neurocognitive impairment associated with predominantly early stage HIV infection in Abuja, Nigeria

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Abstract Detailed neuropsychological testing was performed on 133 human immunodeficiency virus (HIV) seropositive (SP) and 77 HIV seronegative (SN) individuals, 86 % with early stage HIV infection in Nigeria, to determine the frequency of HIV-related neurocognitive impairment among the HIV-infected group. The tests were administered to assess the following seven ability domains: speed of information processing, attention/working memory, executive functioning, learning, memory, verbal fluency, and motor function motor. Demographically corrected individual test scores and scores for each domain or reflecting a global deficit (a global deficit score, or GDS) were compared for the SP and SN groups. SP participants were older, had fewer years of education, were more likely to be married, differed in ethnicity, and had higher depression scores than SN individuals. Within the seven ability domains, SP performed worse than SN with respect to speed of information processing, executive function, learning, memory, and verbal fluency and also on the global measure. SP were also more frequently impaired on tests of SIP, and there was a borderline increase in the frequency of global impairment. On the individual tests, SP performed worse than SN on four tests that assessed learning, verbal fluency, memory, and motor functio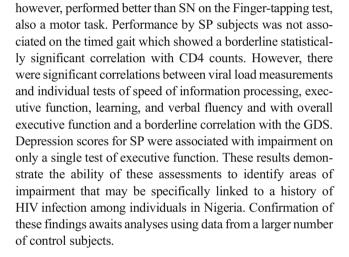n (the Timed Gait). SP subjects, however, performed better than SN on the Finger-tapping test, also a motor task. Performance by SP subjects was not associated on the timed gait which showed a borderline statistically significant correlation with CD4 counts. However, there were significant correlations between viral load measurements and individual tests of speed of information processing, executive function, learning, and verbal fluency and with overall executive function and a borderline correlation with the GDS. Depression scores for SP were associated with impairment on only a single test of executive function. These results demonstrate the ability of these assessments to identify areas of impairment that may be specifically linked to a history of HIV infection among individuals in Nigeria. Confirmation of these findings awaits analyses using data from a larger number of control subjects.

Keywords Neuropsychological · AIDS · Africa

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Introduction

At the end of 2011, 34.0 million people globally were reported to be living with the human immunodeficiency virus (HIV) infection (UNAIDS 2012). Among adults aged 15–49 years worldwide, an estimated 0.8 % is living with HIV infection, with the numbers of infected individuals showing considerable variation between countries and regions. Africa currently accounts for 69.0 % of people living with HIV infection worldwide (UNAIDS 2012). In Nigeria, the number of people living with the infection increased over the 26-year period beginning in 1986, when the first case of AIDS was reported in the country, through December 2011 to about 3.4 million (NACA 2012).

HIV affects virtually all body systems, and the nervous system is a frequent target of infection (Berger et al. 1987; Grant et al. 1987, 1995; McArthur 1987; Snider et al. 1983).

Involvement of the nervous system by HIV infection is associated with an increased risk for the development of neurocognitive impairment (NCI) that occurs in the context of HIV-associated neurocognitive disorders (HAND) (Antinori et al. 2007). The occurrence of NCI in HIV infection can result from either direct mechanisms, for example, neurotoxicity induced by HIV proteins, or due to indirect involvement of the brain, as occurs with bystander damage induced by inflammatory mediators released by activated immune cells or astrocytes (Anderson et al. 2002; Nath 2002). The impact of NCI on the ability of an individual to function can be severe and, untreated, is associated with an increased mortality (Ellis et al. 1997; Mayeux et al. 1993; McArthur et al. 1993). Therefore, NCI ranks as potentially one of the most devastating manifestations of HIV infection. With the introduction of effective combination antiretroviral therapy, the overall incidence on the most severe forms of NCI has decreased, an effect from treatment that has been observed worldwide, including in sub-Saharan Africa (Joska 2010). However, such treatment typically results in an incomplete clinical response, and this fact combined with the improved overall survival from HIV infection has resulted in an increased overall prevalence of NCI (Dore et al. 1999, 2003; Heaton et al. 2011; Sacktor et al. 2001).

There is paucity information regarding the frequency of HIV-associated NCI in Nigeria, where there is a high burden of HIV infection. This report described the results of an analysis of neuropsychological test data from individuals in Abuja, Nigeria, who were recruited into a longitudinal study that will examine factors that are associated with risk for developing neurocognitive impairment as a result of HIV infection.

Results

Demographic, clinical, and laboratory characteristics of study participants

Baseline data available on 210 participants (133 seropositive (SP) and 77 seronegative (SN)) were analyzed. SP participants were overall older and had fewer years of education than SN individuals (Table 1). SP participants were also more likely to be married, to be from different ethnic groups in Nigeria, and to have higher depression scores than SN individuals. SP individuals had lower CD4+ T cell counts than SN, and approximately 86 % of HIV-infected individuals were asymptomatic for their HIV infection. The mean plasma viral load among the 117 SP subjects who were tested was approximately 27,000 copies/ml, and plasma virus was undetectable (<20 copies/ml) in three individuals.

Comparison of domain-specific and overall performance by SP and SN participants on the neuropsychological tests

In order to link neuropsychological test performance to deficit, age and education-adjusted standardized T scores were converted to clinical deficit scores. The mean deficit scores for the seven ability domains and the global deficit score (GDS) were then compared for the SP and SN participants (Table 2). This analysis showed that mean scores for speed of information processing, executive functioning, learning, memory, and verbal fluency were higher for SP than for SN participants. Also, mean GDS was higher for SP than for SN participants.

Analysis of the percentage of individuals with specific ability domain and with global impairment

The percentage individuals who showed evidence of impairment in any of the seven ability domains, indicated by a deficit score >0.5, and the presence of NCI, indicated by a GDS ≥0.5, was compared for the SP and SN groups (Table 3). This analysis showed a statistically significant difference only with respect to speed of information processing, with a higher percentage of SP individuals demonstrating impairment than SN subjects. There was also a borderline increase in the frequency of global impairment among SP participants.

Comparison of SP and SN participant performance on the individual neuropsychological tests

The means of the standardized T scores for the individual neuropsychological tests were compared for SP and SN participants (Table 4). Analysis of the means of the demographically adjusted scores showed that SP participants performed worse on tests of learning (Hopkins Verbal Learning Test-Revised (HVLT-R) total learning), memory (HVLT-R delayed recall), verbal fluency Letter (Word-Sound) Fluency and with motor speed and dexterity (the timed gait test). SN participants performed worse than SP on the finger-tapping test, a test of motor speed and dexterity.

Neuropsychological test result associations with HIV infection parameters and with depression

Correlation analysis was performed to determine whether performance on the neuropsychological assessments was associated with CD4+ T cell counts (<200, 200–500, or >500 μl/dl), HIV clinical status, or with depression. For CD4+ T cell counts, a correlation was observed with the Timed Gait that was of borderline statistical significance (Table 5). Viral load measures, however, showed significant inverse correlations with individual tests of speed of information processing (WAIS-III digit symbol), executive functions (Stroop Color and Word

Table 1 Demographic characteristics, WHO stage, and CD4 count for the HIV seropositive and seronegative subjects

Group	HIV SN	HIV SP	P values
Number of subjects	77	133	
Age (years)			
Mean (SD)[a]	29.48 (6.72)	33.59 (7.28)	<0.0001
Gender (%)			
Female	48 (62.34)	77 (57.89)	0.5
Mean years of education (SD)	14.32 (1.74)	12.39 (3.06)	<0.0001
Number of participants by			
Ethnicity (%)			
Hausa	1 (1.30)	9 (6.77)	0.01
Ibo	11 (14.29)	34 (25.56)	
Yoruba	16 (20.78)	12 (9.02)	
Other[b]	49 (63.64)	78 (58.65)	
Marital status (%)			
Married	27 (35.06)	68 (51.13)	0.024
Single/widowed/divorced	50 (64.94)	66 (48.87)	
WHO Stage (%)	–		
Stage 1		86.47	
Stage 4		8.27	
Stage 3		3.76	
Stage 4		1.50	
Median CD4 count (IQR)[c]	754 (545–883)	348 (217–496.5)	<0.0001
CD4 group (%)			
≤350/μl	3 (3.90)	69 (51.88)	<0.0001
350–500/μl	13 (16.88)	32 (24.06)	
≥500/μl	61 (79.22)	32 (24.06)	
Log HIV viral load (N=117)		4.43 (0.98)	
Median HIV viral load (IQR)		4.56 (3.96–5.08)	
BDI	4.06 (4.42)	7.02 (7.37)	

p= 0.0004 above refers to the result of comparing BDI for SP and SN

[a] SD standard deviation

[b] This category includes a total of 61 ethnic groups, 29 among SN and 32 among SP participants. Eight of the ethnic groups included both SN and SP individuals

[c] IQR Interquartile Range

Table 2 Comparison of mean ability domain and global deficit scores for HIV-1 seropositive and seronegative subjects

	HIV SN	HIV SP	P value
Ability domain deficit scores			
Speed of information processing	0.26 (0.39)[a]	0.47 (0.54)	0.0008
Attention/working memory	0.26 (0.52)	0.26 (0.48)	1.0
Executive function	0.27 (0.46)	0.55 (0.79)	0.0014
Learning	0.25 (0.50)	0.47 (0.71)	0.0082
Memory	0.29 (0.48)	0.45 (0.71)	0.056
Verbal fluency	0.25 (0.44)	0.40 (0.58)	0.029
Motor function	0.25 (0.37)	0.26 (0.37)	0.85
Global deficit score	0.26 (0.23)	0.40 (0.35)	0.0007

[a] Mean (SD)

Table 3 Frequency of impairment in the individual ability domains and globally among study participants

	HIV SN	HIV SP	P value
Ability domain deficit scores			
Speed of information processing	13 (16.88)	52 (39.10)	0.0008
Attention/working memory	22 (28.57)	41 (30.83)	0.73
Executive function	26 (33.77)	60 (45.11)	0.11
Learning	22 (28.57)	54 (40.60)	0.08
Memory	25 (32.47)	50 (37.59)	0.46
Verbal fluency	19 (24.68)[a]	44 (33.08)	0.20
Motor function	15 (19.48)	24 (1805)	0.80
Global deficit score	15 (19.48)	41 (30.83)	0.073

[a] Number impaired (percent)

Table 4 Performance by HIV-1 SP versus HIV-1 SN Participants on the Individual Neuropsychological Tests

	Mean T score[a]	SD	P value	Cohen's d
Speed of information processing				
WAIS-III Digit Symbol	47.99	10.80	0.18	0.19
WAIS-III Symbol Search	47.74	11.96	0.16	0.21
Color Trails Test trial 1	49.80	13.24	0.90	0.02
Trail Making Test A	48.80	14.02	0.47	0.10
Attention/working memory				
Paced Auditory Serial Addition Task	48.64	10.01	0.35	0.14
WMS-III Spatial Span	50.76	10.86	0.61	−0.07
Executive functions				
Color Trails Test trail 2	49.44	12.20	0.73	0.05
Stroop Color and Word Test	48.18	11.07	0.24	0.17
Learning				
HVLT-R total learning	45.08	9.73	0.0006	0.50
BVMT-R total learning	49.82	12.04	0.91	0.02
Memory				
HVLT-R delayed recall	45.46	9.63	0.001	0.46
BVMT-R delayed recall	49.23	13.22	0.96	0.07
Verbal fluency				
Letter (Word Sound) Fluency	45.43	10.26	0.001	0.45
Category Fluency: Nouns (Animals)	48.40	10.23	0.28	0.16
Category Fluency: Verbs (Actions)	48.71	10.54	0.38	0.13
Motor speed and dexterity				
Grooved Pegboard Test	51.92	11.01	0.21	−0.18
Finger Tapping Test	54.98	13.42	0.0025	−0.42
Timed Gait	46.73	10.43	0.027	0.32

[a] All T scores are demographically corrected. T scores were also scaled to yield, for all tests for SN controls, a mean=50 and a standard deviation (SD)=10. A T score <50 indicates worse performance on the testing

Test), learning (HVLT-R total learning) and verbal fluency (Category Fluency: Nouns (Animals), and Category Fluency: Verbs (Actions)). Viral load measurements also showed a significant direct correlation with overall executive function and a borderline significant direct correlation with GDS (Table 5).

Correlations with depression scores were determined for both SN and SP individuals. Scores for SN showed a significant correlation only with the Timed Gait. Depression scores for SP correlated inversely with performance on the Stroop Color and Word Test and, at a borderline level of significance, with overall motor function.

Discussion

This is one of several studies that have examined the frequency of neurocognitive impairment among HIV-infected individuals in Nigeria. Previously, such studies have utilized either the community screening interview for dementia (CSI 'D') or, in studies that we previously reported, the International HIV Dementia Scale (IHDS) (Hall et al. 2000; Odiase et al. 2006; Royal et al. 2012; Salawu et al. 2008). Infected individuals studied using both approaches showed evidence of worse cognitive status as compared to SN

subjects. However, these screens, though useful for identifying abnormalities that occur commonly in HIV infection and take relatively little time to administer, are less sensitive and specific than more detailed neuropsychological testing for detecting HIV-related cognitive impairment.

Preliminary studies performed on small numbers of patients established the feasibility of using a comprehensive neuropsychological test battery for the studies described in this report (Royal et al. 2012). In the study reported here, we found that SP participants performed worse on the BVMT-R total learning, the HVLT-R delayed recall, the Letter (Word-Sound) Fluency tests, and the Timed Gait. Averaging the results of the individual test scores showed that the SP participants performed worse than SN in all of the associated domains, with the exception of that for motor function. Motor impairment can occur in the context of HIV-related cognitive impairment, and such impairment tends to be a later manifestation of HIV nervous system involvement (Antinori et al. 2007; Report of a Working Group of the American Academy of Neurology AIDS Task Force 1991). The reason why SP would perform better on this test is unclear. Perhaps their performance may reflect an ability that is linked to an occupation or other activity that is more typical of individuals in the SP group.

Table 5 Correlations for HIV disease parameters and depression scores with neuropsychological test scores

	CD4	Viral load	BDI	
	SP	SP	SN	SP
I. Individual neuropsychological test *T* scores				
Speed of information processing				
WAIS-III Digit Symbol	0.03, 0.7	−0.203, 0.03	0.15, 0.2	0.06, 0.5
WAIS-III Symbol Search	−0.02, 0.8	−0.157, 0.10	0.03, 0.8	−0.12, 0.17
Color Trails Test trial 1	0.06, 0.5	−0.034, 0.72	0.219, 0.54	−0.02, 0.8
Trail Making Test A	0.06, 0.5	−0.062, 0.51	0.03, 0.8	−0.07, 0.4
Attention/working memory				
Paced Auditory Serial Addition Task	0.03, 0.8	−0.125, 0.19	−0.16, 0.15	−0.03, 0.7
WMS-III Spatial Span	0.03,0.7	0.0003, 1.0	−0.04, 0.8	0.02, 0.8
Executive functions				
Color Trails Test trail 2	−0.04, 0.7	−0.053, 0.58	0.15, 0.2	0.005, 0.95
Stroop Color and Word Test	−0.02, 0.8	−0.199, 0.03	−0.05, 0.6	−0.207, 0.017
Learning				
HVLT-R total learning	−0.01, 0.9	−0.212, 0.024	0.04, 0.7	−0.09, 0.3
BVMT-R total learning	−0.02, 0.8	−0.084, 0.38	−0.02, 0.9	−0.1, 0.3
Memory				
HVLT-R delayed recall	0.06, 0.5	−0.119, 0.21	−0.008, 0.9	0.09, 0.3
BVMT-R delayed recall	0.008, 0.9	−0.090, 0.34	0.04, 0.8	−0.05, 0.6
Verbal fluency				
Letter (Word Sound) Fluency	0.13, 0.14	−0.204, 0.029	0.03, 0.8	0.07, 0.4
Category Fluency: Nouns (Animals)	0.04, 0.7	−0.163, 0.08	0.06, 0.6	−0.09, 0.3
Category Fluency: Verbs (Actions)	0.17, 0.2	−0.234, 0.012	−0.07, 0.5	−0.04, 0.6
Motor function				
Grooved Pegboard Test	−0.06, 0.5	−0.079, 0.40	0.20, 0.09	−0.14, 0.1
Finger Tapping Test	0.06, 0.5	−0.026, 0.78	−0.10, 0.4	−0.04, 0.6
Timed Gait	0.162, 0.06	−0.113, 0.3	−0.367, 0.0013	−0.1, 0.3
II. Ability domain deficit scores[a]				
Speed of information processing	−0.02, 0.8	0.114, 0.23	−0.19, 1.0	0.1, 0.3
Attention/working memory	−0.02, 0.8	0.073, 0.44	0.08, 0.5	0.004, 0.97
Executive functions	0.03, 0.7	0.247, 0.008	0.08, 0.5	0.09, 0.3
Learning	−0.01, 0.9	0.84, 0.37	0.09, 0.4	0.12, 0.2
Memory	−0.05, 0.6	0.015, 0.88	−0.15, 0.2	0.08, 0.4
Verbal fluency	−0.15, 0.08	0.137, 0.15	−0.20, 0.08	0.02, 0.8
Motor function	−0.09, 0.3	0.062, 0.51	0.12, 0.3	0.156, 0.073
III. Global deficit score	−0.08, 0.3	0.172, 0.067	−0.05, 0.6	0.14, 0.11

[a] Correlation coefficient, *p* value

In contrast to the relatively low frequency of impairment on the individual tests, a difference in mean disability scores was noted for five of the seven ability domains, and a significant difference was also noted for the mean GDS (Table 3). In addition, there were increased frequencies of impairment in one domain and with respect to the GDS. Similar domain-specific and overall differences have been previously reported when comparing SP and SN subjects in both African and Western cohorts (Heaton et al. 2011; Kanmogne et al. 2010). However, it is notable in our data that few individuals scored beyond the defined cutoffs for impairment for the domain scores and for the GDS. This is consistent with the fact that the SP participants were overall in the early stages of their HIV disease.

To determine whether measures of HIV disease status might have impacted performance of the testing, correlations between CD4+ T cell counts and viral load with individual neuropsychological test, domain, and global scores were examined. The level of immunosuppression as indicated by the CD4+ T cell count appeared to have little impact on performance on the outcome of the testing. However, a higher viral load was associated with impaired performance on multiple tests within several domains and with respect to global neurocognitive functioning. These findings suggest that more subtle viral

effects on test performance may be observed even where there may be few individuals who perform in a range where they would be considered to be impaired. Such associations may in some individuals be potentially linked to the milder forms of HAND (i.e., asymptomatic neurocognitive impairment or minor neurocognitive disorder). Which SP individuals in the study met criteria for the various subtypes of HAND were not determined for this report; however, this will be the focus of future analyses. Of note is the fact that the presence of depressive symptoms among members of the cohort did not appear to have an impact on how well individuals performed in the testing.

Despite the several interesting observations described above, there are several limitations to our study. A significant limitation is the fact that, although scores were adjusted for age and education, the number of individuals in the control group is less than what is generally considered ideal to be able to adequately control for these factors. With respect to the reported number of years of education, it is the case that in some African communities much education occurs in the home with the elderly teaching the young. Therefore, the number of years of formal education may not accurately reflect the level of education that is actually achieved by an individual (Paddick et al. 2013). In addition, the education background of the participant will, to some extent, reflect the population of patients that seek care at the health care centers where the recruitment for the study took place. The same limitation can be also stated for other participant demographic factors. One approach to addressing these issues would have been to match the groups on these variables. While this can be considered for future analyses, recruitment of SN subjects into the study has continued and repeat analyses are planned that will utilize a larger number of controls. Such studies should provide even more reliable normative data. Future studies using such norms may, indeed, yield findings that are different from what is reported here. However, the fact that our overall results are consistent with what has been previously reported gives confidence that it is unlikely that major differences from what we present here will emerge. It is also not always possible to control for certain factors that may be important, which is the case for the differences noted in the ethnicity of the SP and SN subjects. The major groups are represented in the categorization that is presented; however, a significant percentage falls outside of these groups. This reflects the fact that a large number of ethnic groups exist in Nigeria. To try to place each person in our study in a separate group would have yielded only one or two individuals in some groups, and to exclude such individuals from the study would have resulted in the cohort not being reflective of the ethnic diversity of the general population. Other important issues that were not addressed in this report are the likely role of strains of HIV that are present in Nigeria, and possible host factors that may influence the expression and course of disease. Such information, combined with those from the studies described here, is likely to be valuable for understanding patterns of treatment responses and the overall effectiveness of such approaches as there continues to be a rapid scale up of treatment with antiretroviral agents in Nigeria.

Materials and methods

Study recruitment and participants

Study participants were recruited from two clinical sites, the National Hospital (NH) and the University of Abuja Teaching Hospital (UATH), in Abuja, the capital city of Nigeria. These hospitals are within a network of sites supported by the Institute of Human Virology, Nigeria (IHVN) with funds from the US President's Emergency Plan for AIDS Relief (PEPFAR) program. SP subjects were recruited at the time of a regular clinical visit. SN controls were recruited from the HIV voluntary counseling and testing centers located at the clinical sites where HIV patients are recruited. At the time of standard post-test counseling, HIV negative subjects were individually and privately invited to speak with a study staff member who performed screening for eligibility employing the process described above. All individuals were ≥18 years of age, able to converse in English, and antiretroviral-naive with no history of active tuberculosis, syphilis, or other infections. The participants also had no evidence of the presence of a clinical problem that could impair their ability to participate in the testing, including active CNS or systemic disease, a history of significant head trauma, a history or alcohol abuse, use of other mind-altering substances, or if there was evidence of substance use on urine toxicology screening, a previous diagnosis of a learning disability or psychiatric disorder, or other disorders associated with the presence of focal neurological signs or deficits. Demographic information was obtained, and participants were administered standardized questionnaires, a thorough general medical assessment, and neuropsychological testing (described below). Volunteers underwent phlebotomy and subsequent determination of HIV-1 serological status and measurement of CD4+ T cell count performed at the IHVN-supported Research Laboratory located in Asokoro, Abuja. Viral load measurements were performed using the Roche Amplicor Monitor Test v.1.5 (Roche; detection range=400–750,000 copies/ml, or the COBAS® AmpliPrep/COBAS TaqMan HIV-1 Test (Roche; detection range=20–10,000,000 copies/ml). Informed consent was obtained from the study participants independently or with the assistance of a family member. All study procedures were approved by the University of Maryland Baltimore, NH, and UATH Institutional Review Boards and by the Nigerian National Health Research Ethics Committee. The enrollment target for the study has been set at 100 SN and 200 SP individuals.
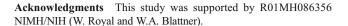
Neuropsychological testing

A detailed standardized neuropsychological battery was administered to all study participants in order to identify possible impairment within specific cognitive domains of interest. The testing was administered at each of the testing site by either of two nurses who underwent training in Nigeria administered in-person by a University of California, San Diego (UCSD) neuropsychological testing technician. For quality control, the tests were double-scored, and completed forms on randomly selected participants were assessed for accuracy and discussed at a monthly teleconference. The ability domains tested (followed by the individual tests within the domains in parentheses) were speed of information processing (WAIS-III Digit Symbol, WAIS-III Symbol Search, color trails test trail 1, and Trail-Making Test A); attention/working memory (Paced Auditory Serial Addition Task and WMS-III Spatial Span); executive functioning (Color Trails Test Trial 2 and Stroop Color and Word Test), learning ((Hopkins Verbal Learning Test-Revised (HVLT-R) total learning, and Brief Visuospatial Memory Test-Revised (BVMT-R) total learning)); memory (HVLT-R delayed recall and BVMT-R delayed recall), verbal fluency (Letter (Word Sound) Fluency, Category Fluency: Nouns (Animals), and Category Fluency: Verbs (Actions)); motor function (Grooved Pegboard Test, Finger-Tapping Test, and Timed Gait) and screening for effort (Hiscock Digit Memory Test). Raw scores from the neuropsychological tests were converted to standardized scores (T scores) that were adjusted for age, gender, and education based on the SN sample. T scores were then used to calculate a global deficit score (GDS), reflecting performance across the test battery, with a score ≥ 0.5 indicating NCI (Carey et al. 2004). In addition to recruiting only English speakers, to minimize the potential impact of language of cultural differences on performance on the testing, words were eliminated from verbal tests that were likely to be unfamiliar to individuals from the region and, after appropriate pilot testing, were replaced by more familiar terms.

Statistical analysis

Demographic data and neuropsychological T scores and global deficit scores were compared for SP and SN participants using t tests or the Mann-Whitney U test, as appropriate. The frequency of impairment and selected categorical demographic and clinical data were compared for the two groups using the chi-square test. Neuropsychological test score associations with CD4+ T cell counts viral load and depression scores and GDS were examined using regression analysis. Correlations were examined by calculating the Pearson's correlation coefficient or Spearman's rank correlation coefficient, as appropriate.

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