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Neurocognitive Impairment in HIV-1 Clade C versus B Infected Individuals in Southern Brazil

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Abstract

HIV-1 clade C isolates show reduced Tat protein chemoattractant activity compared with clade B. This might influence neuropathogenesis by altering trafficking of monocytes into the CNS. A previous study suggested low rates of HIV-associated dementia in clade C infected individuals. The present study evaluated neurocognitive impairment rates in clade B- and C-infected individuals from the same local population. HIV+ and HIV- participants were recruited from the same geographic region in southern Brazil. We evaluated neuropsychological (NP) impairment using a screening instrument (the International HIV Dementia Scale; IHDS), as well as a Brazilian Portuguese adaptation of a comprehensive battery that has demonstrated sensitivity to HIV associated neurocognitive disorders (HAND) internationally. NP performance in controls was used to generate T-scores and impairment ratings by the global deficit score (GDS) method. Clade assignments were ascertained by sequencing *pol* and *env*. Blood and cerebrospinal fluid (CSF) were collected from all HIV+ participants. HIV+ and HIV- participants were comparable on demographic characteristics. HIV+ participants overall were more likely to be impaired than HIV- by the IHDS and the GDS. Clade B and C infected individuals were demographically similar and did not differ significantly in rates of impairment. The prevalence of pleocytosis, a marker of intrathecal cellular chemotaxis, also did not differ between clade B and C infections. Clade B and C HIV-infected individuals from the same geographic region, when ascertained using comparable methods, did not differ in their rates of neurocognitive impairment, and there was no evidence of differences in CNS chemotaxis.

Keywords

HIV-associated neurocognitive disorders (HAND); HIV-1; clade; dementia; cerebrospinal fluid

Introduction

Numerous studies have demonstrated high rates of neurocognitive impairment (15 -50%) among individuals with HIV infection in the U.S., Europe and several other geographic regions where clade B infections predominate. Neurocognitive impairment has been less

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intensively studied in non-clade B HIV-1 infections. However, some studies report differences in impairment rates according to clade (Sacktor *et al*, 2009). Clade C is the most common HIV-1 subtype worldwide. In vitro, clade C isolates show reduced Tat protein chemoattractant activity compared with clade B, a characteristic that has been attributed to a single amino acid substitution in the conserved cysteine-rich domain of the Tat protein (Ranga *et al*, 2004). This substitution may attenuate Tat neurotoxicity (Mishra *et al*, 2008), potentially lowering the rate of neurocognitive impairment in clade C. However, rates of neurocognitive impairment can be influenced by numerous factors, including method of ascertainment and presence of comorbid conditions such as brain injury and infections other than HIV. Thus comparisons of clade effects across geographic regions and using different ascertainment methods are difficult to interpret.

In a molecular epidemiological analysis of 245 adults with HIV-1 infection from the state of Paraná, Southern Brazil from 1999-2007, the distribution of clades was as follows: B 140 (57%), C 67 (23%), F 24 (10%) and mosaic or unique recombinant forms (URFs) 24 (10%) (Raboni *et al*, 2010). These data indicate substantial co-occurrence of clade B and C in the same regional population. The purpose of the present study was to take advantage of this co-occurrence to determine whether neurocognitive impairment rates differ in clade C vs. clade B infections in the same regional population. We also sought to demonstrate the cross-cultural applicability in Brazil of an NP test battery validated for detecting and characterizing HIV in the U.S. and elsewhere (Cameroon, China, India, Romania, Zambia). Finally, to evaluate the potential impact of differences in clade C Tat, we sought to compare rates of cerebrospinal fluid (CSF) pleocytosis -- a marker of intrathecal chemotaxis -- in clade B and C infections.

Methods

This cross-sectional study performed standardized clinical and neurocognitive evaluations on prospectively enrolled HIV+ and HIV- individuals in Southern Brazil. HIV+ participants were recruited from the Hospital de Clinicas UFPR (HC-UFPR), Curitiba, Brazil. Control participants were recruited from the HC-UFPR blood bank and tested serologically negative for HIV, HBV, HCV and syphilis. HIV+ and HIV- groups were group-matched for sex, age and years of education. The HC-UFPR Institutional Review Board (IRB) and the National ethics committee approved this project. Written informed consent was obtained from study participants after the research procedure had been fully explained to them. Participants were not reimbursed for their time.

Individuals with a known history of non-HIV-related neuromedical factors that might potentially cause impairment of neurocognitive function were excluded. These exclusion criteria consisted of brain injury with unconsciousness greater than 30 minutes, and any known, non- HIV-related neurological disorders (e.g., epilepsy, stroke), psychotic disorders (schizophrenia and bipolar disorder), and potentially significant levels of current substance use, defined as more than two alcoholic drinks per day over the past 30 days, or use of any illegal drugs in the past 30 days.

HIV serostatus and clade typing

All HIV+ participants received serological testing to confirm their HIV status before enrollment according to guidelines published by the Brazilian Ministry of Health (BRASIL, 2009). For participants who had clinical resistance genotyping (RENAGENO), HIV subtype (clade) was assigned using *pol* sequences. For the remainder, subtype was determined by sequencing *env* from HIV DNA, yielding 25 clade C and 27 clade B infections. Low frequency infections with clade F (N=1) or recombinants (BF, N=10; CF, N=1) were not included in this analysis. Subtype could not be identified for 4 additional subjects.

Neuromedical (NM) assessments

Participants underwent a comprehensive neuromedical assessment. This included a blood draw, lumbar puncture (HIV+ only), neurological examination and administration of the International HIV Dementia Scale (IHDS). HIV RNA was assessed in blood and CSF using the BDNA Siemens assay. Among HIV+ participants, hepatitis C virus (HCV) serostatus was assessed using HCV antibody testing (Abbott-Architect). HIV- individuals with hepatitis C, syphilis or HTLV were excluded based on blood donor testing.

Neurobehavioral Assessments

The NP test battery assessed 7 domains and comprised 15 individual NP measures (Table 1) widely used to study HIV infection in the United States (Carey *et al*, 2004) (Woods *et al*, 2004), Europe (Tozzi *et al*, 2007), Australia (Cysique *et al*, 2006), and in multinational studies. The instruments were translated into Portguese, back-translated into English, and reviewed by several Brazilian native Portuguese speakers to ensure cultural and linguistic appropriateness.

To explore the clinical significance of any NP impairment, we assessed self-reported cognitive difficulties in everyday life, as well as degree of independence in instrumental activities of daily living (IADL), and employment status using Portuguese translations of standard English instruments. Subjective neurocognitive difficulties were assessed using the Patient's Assessment of Own Functioning Inventory (PAOFI) (Chelune *et al*, 1986). The PAOFI includes 33 items on which participants rate themselves as having or not having neurobehavioral difficulties in their everyday lives, using a 6-point scale, in domains of memory, language and communication, sensory-perceptual and motor skills, and higher level cognitive functions. The score used is the sum of items on which the participants reported experiencing difficulties as either “fairly often,” “very often,” or “almost always” (Chelune *et al*, 1986). Employment status was derived from the extended demographic interview, which collected information on whether the participant is currently working, as well as type of employment, and income. A modified version of the Lawton and Brody IADL scale was used to assess degree of current independence in activities of daily living compared to best previous level (Heaton *et al*, 2004).

Participants completed the Beck Depression Inventory-II (BDI-II) (Beck *et al*, 1996). The BDI-II is a 21-item self-report measure that rates severity of depressive symptoms during the past week, addressing somatic (e.g., weight loss, fatigue) and nonsomatic (e.g., suicidal ideation, feelings of guilt) depressive symptoms; higher scores indicate worse depressive symptomatology.

HAND diagnosis

HAND diagnoses were assigned according to the Frascati Criteria (Antinori *et al*, 2007). Briefly, all impaired participants received neurocognitive confounding classifications as previously described: severe (confounding), moderate (contributing) or minimal (incidental) neurocognitive comorbidities. Participants with severe neurocognitive comorbidities were not eligible for a diagnosis of HAND. To receive a diagnosis of HIV-associated dementia (HAD), subjects had to have moderate-to-severe impairment and require major assistance in activities of daily living. Minor neurocognitive disorder (MND) was diagnosed when NP impairment was mild-to-moderate and difficulties were reported in 2 PAOFI areas, except that for participants with significant depressive symptomatology), 3 PAOFI areas were required. Remaining NP impaired participants with mild-to-moderate impairment were assigned a diagnosis of asymptomatic neurocognitive impairment (ANI).

Quality Control Procedures

Quality assurance reviews were conducted on test forms for all participants. Copies of the entire battery were sent to the United States and reviewed for administration and scoring accuracy, form completion, and overall quality of data. All queries and data changes were sent to the Brazil team for correction of the raw data as well as data entry.

Examiner Training

To ensure standardization of NP test administration, examiners (psychologists at UFPR) underwent training done by the UCSD team from the United States, with at least one bilingual member to facilitate discussion. During the training session, each test or interview was demonstrated, and its purpose and administration nuances were discussed. Several rounds of “mock testing” were conducted. Certification sessions subsequently took place using staff or patient volunteers from the hospital as test subjects. There were separate training teams for the neurobehavioral, neuromedical, and psychiatric modules of the battery. All certifications were done in Portuguese.

Development of Neuropsychological Test Norms

Demographically corrected norms for each NP test were developed using data from Brazilian HIV- controls. Norms were statistically derived by methods previously described(Heaton *et al*, 2004). Briefly, raw scores on the individual tests were placed on a common metric, specifically, normally distributed scaled scores, which have a mean of 10 and a standard deviation of 3. The scaled scores were then converted to T-scores (mean 50, SD 10), controlling for demographic data (age, education, and gender) by generating fractional polynomial regression equations for demographic correction. Optimal fractional polynomial equations were determined using the method of Royston and Altman (Royston and Altman, 1994) in R (www.R-project.org). Global and domain mean T-scores were computed. Additionally, the Global Deficit Score (GDS) method was used to classify overall NP impairment status as previously described (Carey *et al*, 2004; Heaton *et al*, 2004). For each test, T-scores were converted to deficit scores as follows: T>39 (normal); 35-39 (mild impairment); 30-34 (mild to moderate impairment); 25-29 (moderate impairment); 20-24 (moderate to severe impairment); T<20 (severe impairment). Deficit scores were summed across the test battery and then divided by the number of individual measures to compute the GDS. The GDS summarizes the number and severity of neurobehavioral deficits across the entire test battery. Additionally, a GDS cut-off of <0.50 was used to classify overall NP impairment (Carey *et al*, 2004; Heaton *et al*, 2004).

Statistical analysis

Comparisons between groups were made using chi-square tests, Fisher's exact tests, t tests, and analyses of variance (ANOVAs) as appropriate. 95% confidence intervals for proportions impaired were calculated using the normal distribution with no continuity correction.

Results

As shown in Table 2, the 52 HIV+ and 48 HIV- participants were well-matched with respect to age, sex, and education. Among HIV+ participants, more than half were women, and the average age and education were 41.6 and 8.5 years, respectively. Most HIV+ participants (40/52; 77%) had AIDS (CD4 nadir < 200 or past major opportunistic disease). ART was prescribed to 36 (69%) of the HIV+ participants, and among these, 23 (64%) were virologically suppressed (plasma HIV RNA < 50 copies/mL). The most frequent (27; 58%) ART regimen contained a ritonavir-boosted HIV protease inhibitor (PI) plus two nucleoside/

nucleotide reverse transcriptase inhibitors (NRTI; NtRTI). An additional 10 participants (28%) received a non-nucleoside RT inhibitor (NNRTI) with 2 NRTIs, and 5 participants received other regimen types. Among HIV+ participants, hepatitis C serology was positive in 8 (15%).

The proportion of NP-impaired participants was significantly higher for HIV+ versus HIV- using both the screening test (IHDS) (score ≤ 10; 37% vs 10%; p=0.004) and comprehensive NP testing (GDS≥0.50; 62% [95% CI 47-74%] versus 23% [95% CI 13-37%]; p=0.0001). As shown in Figure 1, HIV+ participants meeting criteria for an AIDS diagnosis according to 1993 CDC criteria were more frequently impaired than HIV+ individuals without AIDS.

As shown in Table 3, clade B and C infected individuals were similar in age, sex, education, comorbid depression, and hepatitis C virus serostatus. Clade B-infected participants had lower CD4 nadirs (77 versus 174) and longer estimated duration of HIV infection than clade C. Clade B infected participants were non-significantly more likely to be on ART (78% vs 60%; p=0.23), and those on ART were more likely to be virologically suppressed (plasma HIV RNA < 50 copies/mL, 81% vs 40%, p=0.01). NNRTIs were included in 9/21 (43%) of those with clade B infection vs 4/15 (27%) of those with clade C infection (p=0.48).

There was no significant difference in IHDS scores between clade B and clade C infected individuals (11.0 [9.0-12.0] vs. 12 [9.8-12.0]; p=0.21). Applying demographic corrections to the IHDS scores was consistent in showing no difference between the two clades (T-scores 49.7 [41.1, 62.1] versus 54.8 [45.1, 64.0]). Similarly, GDS impairment rates (≥ 0.50) did not differ for the two groups: clade B 65% [95% CI 47-83%] versus clade C 57% [95% CI 38-77%]). After adjusting for ARV status and plasma viral load, impairment rates did not differ between clade B and clade C infected individuals (p=0.91). Regardless of clade, individuals currently taking CART had lower CD4 nadir (median [IQR] 52 [10, 174] versus 376 [217, 556]; p<0.0001) and were more likely to be impaired (23/32 [72%] versus 6/15 [40%]; p=0.036) than those not taking CART.

HAND classifications were assigned for participants who had no confounding neurocognitive comorbidities (Figure 2). Of 26 HAND-eligible clade B participants, 9 (35%) were NP normal, 13 (50%) had ANI, none had MND and 4 had HAD. Of 21 clade C participants, 9 (43%) were NP normal, 10 (48%) had ANI, 1 (5%) had MND and 1 (5%) had HAD. There were no significant differences in HAND diagnoses between the two clades (X^2=2.69; p=0.442) and the frequency of HAD was not different (Fisher's exact, p=0.37).

As shown in Figure 3, the prevalence of pleocytosis (WBC >5), a marker of intrathecal cellular chemotaxis, did not differ between clade B and C infections (6 (22%) vs 8 (32%); X^2=0.631; p=0.43).

Discussion

In southern Brazil, we found that HIV+ individuals were significantly more likely to be neurocognitively impaired than HIV-, as has been demonstrated previously in the U.S., Europe, Asia and Africa. We successfully adapted the HNRP neuropsychological battery for use in Brazilian Portuguese speakers. The impairment rate in HIV+ subjects in Brazil was similar to that found recently in a large, multi-site U.S. study (Heaton *et al*, 2010). The IHDS detected only about half of those who were impaired by a more comprehensive neuropsychological assessment. This is consistent with previous evidence that the IHDS is insensitive to the milder forms of HAND (Sakamoto *et al*, 2012) limiting its value as a screening instrument.

The 23% impairment rate in HIV- controls in this study, using the standard GDS cutoff of ≥0.50, was slightly higher than the expected value of 16%, based on the lower tail of the normal distribution at -1 standard deviation. Since estimated impairment rates based on any given GDS cutoff have an uncertainty that depends upon the number of HIV- controls examined, this higher than expected impairment rate was likely an artifact of the small sample size.

We found that while the NP impairment rate was numerically higher in clade B than C, this difference was not statistically significant. Furthermore, Clade B-infected individuals had longer known duration of HIV infection, lower CD4 nadirs, and were more likely to meet criteria for ART by local treatment guidelines. In previous studies, these indicators of more advanced HIV disease were associated with increased rates of impairment, suggesting that the higher clade B impairment rate in our study might reflect confounding due to differences in disease stage. Indeed, adjusting for these indicators abrogated the numerically higher impairment rate in clade B infections.

Our findings are consistent with those in a previous report that evaluated HIV clade C-infected, antiretroviral naive individuals in South India, reporting an impairment rate of 60.5% (Gupta *et al*, 2007). Our findings differ from previous reports that suggested a lower prevalence of dementia in clade C compared to B. For example, Satishchandra et al. (Satishchandra *et al*, 2000) found only six cases of HIV-associated dementia (HAD) among 427 HIV-infected asymptomatic individuals (1.4%) in India, where nearly all infections are clade C. However, in their study no clade B-infected individuals were directly assessed, and HIV- controls were not evaluated. We believe that our approach has fewer biases than previous reports. Unlike the Satishchandra et al (Satishchandra *et al*, 2000) report we applied a standardized neuropsychological assessment to diagnose neurocognitive impairment, instead of routine neurological examination. Furthermore, we applied identical ascertainment methods to compare impairment rates in clade B and C individuals recruited from the same geographic region, and we included HIV- controls.

Clade C-infected individuals on ART were less likely to have virologic suppression than those with clade B. Although there is some evidence that genotypic and phenotypic resistance to NNRTIs occurs more commonly in clade C than clade B infections (Sucupira *et al*, 2013), relatively fewer clade C participants took regimens that included an NNRTI, arguing against this explanation.

A defective clade C chemotactic motif would be predicted to confer a lower likelihood of CSF pleocytosis. In fact, we showed a nonsignificantly higher frequency of pleocytosis in clade C vs clade B.

In summary, this study showed no significant reduction in neurovirulence or intrathecal chemotaxis for clade C vs. B infections. Future work should evaluate whether clade C Tat in Southern Brazil harbors the same cysteine-serine (CS) motif as was seen in 90% of clade C viruses in India (Ranga *et al*, 2004).

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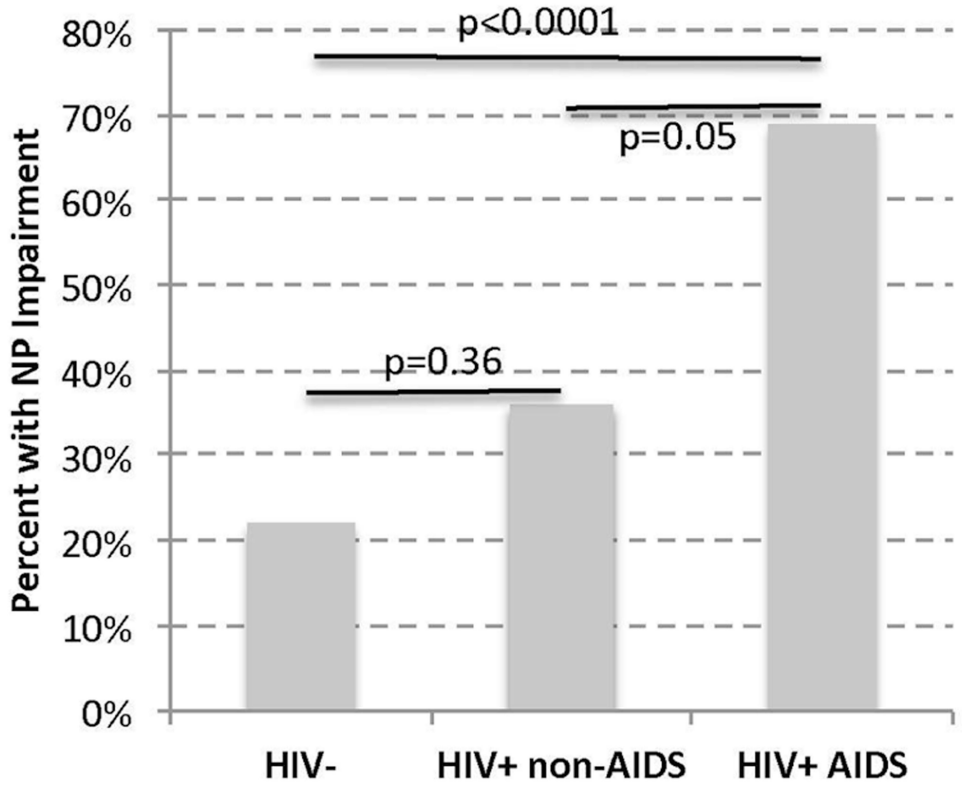

Figure 1.
Proportion of subjects in each group meeting criterion for global neurocognitive impairment.

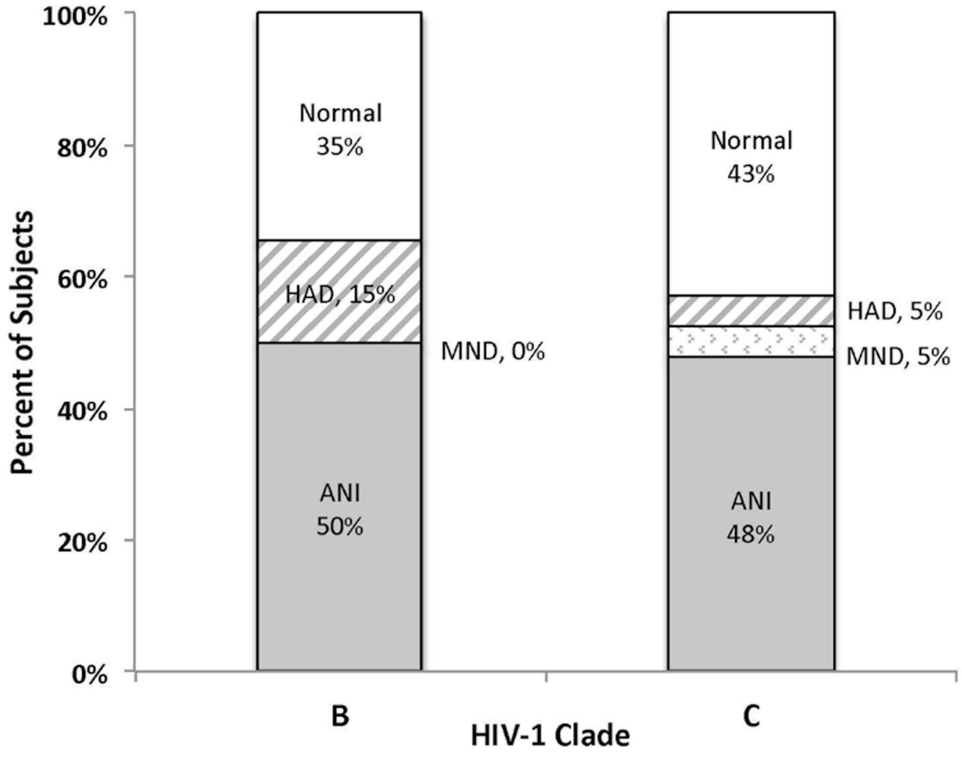

Figure 2.
Diagnostic classification by clade according to criteria for HIV-associated neurocognitive disorders (HAND; Antinori at all 2007).

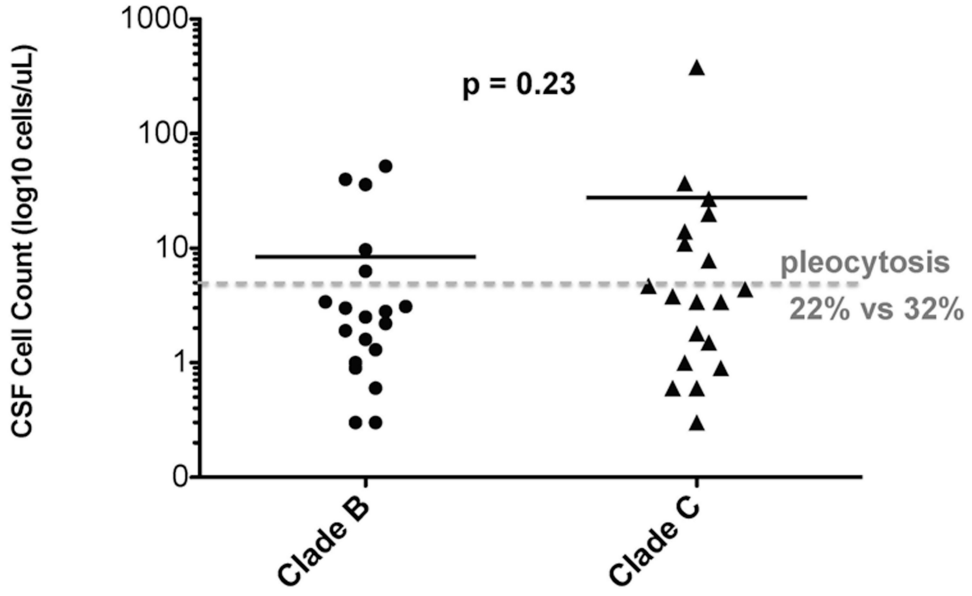

Figure 3.
CSF cell counts according to HIV-1 clade.

Table 1

Neuropsychological Test Battery, by domain.

Verbal Fluency	Attention/Working Memory
Animals	PASAT-50
Action	WMS-III Spatial Span
Motor	Executive Functioning
Grooved Pegboard	WCST-64
Processing Speed	Color Trails II
WAIS-III Digit Symbol	Category Test
WAIS-III Symbol Search	Stroop Color-Word
Color Trails I	Learning/Memory (2 domains)
Trail Making Test A	Verbal (HVLT-R)
Stroop Color Naming	Visual (BVMT-R)

Table 2

Demographic characteristics of HIV+ and HIV- participants.

	HIV+ (n=52)	HIV- (n=48)	p
Age, years – mean (SD)	42.8 (8.8)	42.9 (11.3)	0.97
Education, years– mean (SD)	8.8 (4.3)	9.1 (4.4)	0.76
Sex male - N (%)	24 (46%)	25 (52%)	0.69

Table 3
Demographic and clinical characteristics of HIV+ participants by clade

	Clade B (n=27)	Clade C (n=25)	p
Age years – mean (SD)	43.6 (8.9)	41.3 (8.1)	0.33
Sex male – N (%)	14 (52%)	10 (40%)	0.56
Education yrs -mean (SD)	8.8 (4.8)	8.0 (3.5)	0.49
Disease and Treatment			
On CART – N (%)	21 (78%)	15 (60%)	0.23
Virologically suppressed on CART	17 (81%)	6 (40%)	0.011
Current CD4 – median (IQR)	457 (236-607)	372 (193-473)	0.24
Nadir CD4 – median (IQR)	77 (33-248)	174 (22-360)	0.29
CSF WBC (cells/uL) – median (IQR)	1.6 (0.3-3.4)	3.4 (0.6-11.0)	0.23
Duration of infection (mos)	130 (82-174)	88 (29-140)	0.08
AIDS	81%	72%	0.42
Comorbidities			
HCV antibody positive – N (%)	22%	8%	0.23
Depressive Symptoms - BDI Score	19 (11-28)	14 (7-27)	0.49

CART, combination antiretroviral therapy

Plasma VL ($\log_{10}$ c/mL)