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Attention/working memory, learning and memory in adult Cameroonians: Normative data, effects of HIV infection and viral genotype

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Abstract

OBJECTIVE—There is lack of Cameroonian adult neuropsychological(NP) norms, limited knowledge concerning HIV-associated neurocognitive disorders in Sub-Saharan Africa, and evidence of differential inflammation and disease progression based on viral subtypes. In this study, we developed demographically-corrected norms and assessed HIV and viral genotypes effects on attention/working memory(WM), learning, and memory.

METHOD—We administered two tests of attention/WM [Paced Auditory Serial Addition Test (PASAT)-50, Wechsler Memory Scale(WMS)-III Spatial Span] and two tests of learning and memory [Brief Visuospatial Memory Test-Revised(BVMT-R), Hopkins Verbal Learning Test-Revised(HVLT-R)] to 347 HIV+ and 395 seronegative adult Cameroonians. We assessed the effects of viral factors on neurocognitive performance.

RESULTS—Compared to controls, people living with HIV(PLWH) had significantly lower T-scores on PASAT-50 and attention/WM summary scores, on HVLT-R total learning and learning summary scores, on HVLT-R delayed recall, BVMT-R delayed recall and memory

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Conflicts of Interest

The authors declare that they have no conflict of interest.

summary scores. More PLWH had impairment in attention/WM, learning and memory. ART and current immune status had no effect on T-scores. Compared to untreated cases with detectable viremia, untreated cases with undetectable viremia had significantly lower(worse) T-scores on BVMT-R total learning, BVMT-R delayed recall and memory composite scores. Compared to PLWH infected with other subtypes(41.83%), those infected with HIV-1 CRF02_AG(58.17%) had higher(better) attention/WM T-scores.

CONCLUSIONS—PLWH in Cameroon have impaired attention/WM, learning and memory; and those infected with CRF02_AG viruses showed reduced deficits in attention/WM. The first adult normative standards for assessing attention/WM, learning and memory described, with equations for computing demographically-adjusted T-scores, will facilitate future studies of diseases affecting cognitive function in Cameroonians.

Keywords

Neuropsychological tests; Norms; Sub-Saharan Africa; HIV/AIDS; Subtypes; Neurocognitive impairment

INTRODUCTION

HIV-induced central nervous system (CNS) dysfunction often result in behavioral, motor and cognitive abnormalities termed HIV-associated neurocognitive disorders (HAND) (Antinori et al., 2007). Despite the success of combination antiretroviral therapy (ART) at reducing blood viremia and prolonging the life expectancy of people living with HIV (PLWH), the prevalence of asymptomatic neurocognitive impairment (NCI) and mild neurocognitive disorders (milder forms of HAND) have not decreased (Heaton et al., 2010).

Of the current 38 million PLWH, HIV-1 accounts for >95% of all infections and includes four groups: M (major), O (outlier), N (non-M non-O), and P (LANL, 2017; Robertson DL, 2000). HIV-1 group M accounts for the vast majority of infection globally and includes 9 pure clades (A-D, F-H, J and K), sub-clades (A1 and A2, F1 and F2), about 96 circulating recombinant forms (CRFs) and several unique (unclassified) recombinant forms (URFs) (LANL, 2017, 2019). HIV-1 clade-B is prevalent in Western and central Europe, North America and Australia. Clades A and D are prevalent in East and West Africa and Russia; clade-C is prevalent in Southern Africa and South Asia. Circulating recombinant forms such as CRF02_AG are predominant in West and Central Africa while CRF01_AE is present in Central Africa, Thailand and other Asian countries (Lihana et al., 2012).

Most of the current understanding of HIV neuropathology and HAND comes from studies of Western populations infected with HIV-1 clade-B (K. R. Robertson, Smurzynski, et al., 2007); whereas over two-thirds of the 38 million PLWH are in Sub-Saharan Africa (SSA) and are mostly infected with different (non-B) clades (WHO, 2016). Thus, it is important to investigate the prevalence and risks of NCI in these populations.

Cameroon, like other SSA countries, has been heavily afflicted by the HIV/AIDS pandemic, with an estimated adult prevalence of 3.8% (total population: 25 million) (IndexMundi, 2018). In 2016, Cameroon had an estimated 560,000 PLWH (70% were 15–24 years

old and 65% of infected adults were females) and registered 29,000 HIV/AIDS-related deaths (UNAIDS, 2016). Considering the high HIV genetic diversity and predominance of CRF02_AG infections in Cameroon (Brennan et al., 2008), investigating the effects of viral genotypes on neurocognition would be of great significance.

Cognitive domains often impaired in PLWH include attention/working memory (WM), and episodic memory (new learning and delayed recall). PLWH have significant deficits in episodic memory, significant difficulties in tasks of visual and verbal working memory (Farinpour et al., 2000; Martin et al., 2001; Morgan et al., 2009), and HIV-associated impairment in attention/WM and episodic memory can affect higher-level everyday cognitive functioning such as decision making (Woods et al., 2009). Impairment in attention/WM and episodic memory in PLWH is also associated with difficulties in everyday functioning, including poor medication adherence (Heaton et al., 2004; Levine et al., 2005), and correlates with some measures of disease severity, with increased prevalence of mild-to-moderate deficits observed among patients with a history of severe immunosuppression (Reger et al., 2002).

In a previous pilot study with a limited sample size (44 HIV+ and 44 seronegative controls subjects), we adapted Western neuropsychological (NP) measures to Cameroon and analyses of mean z-scores showed that those tests were appropriate for use in Cameroon (Kanmogne et al., 2010). However, use of NP tests to assess human cognitive abilities require normative standards for the population being assessed. There are no norms for assessing attention/WM, learning, or delayed recall (hereafter called “memory”) in adult Cameroonians. In the present study, we use a larger sample size (347 cases and 395 controls) to establish normative standards for two commonly used NP tests of attention/WM: Paced Auditory Serial Addition Test (PASAT)-50 (Diehr et al., 2003) and Wechsler Memory Scale (WMS)-III Spatial Span (Wechsler, 1997); and two commonly used NP tests of learning and memory: Brief Visuospatial Memory Test-Revised (BVMT-R) (R. Benedict, 1997) and Hopkins verbal learning test-revised (HVLT-R) (Brandt, 2001). We developed demographically-adjusted normative standards for Cameroon and assessed the effects of HIV infection, current immune status, treatment, and viremia on NP performance. Because inflammation plays a major role in HAND pathogenesis (Hong & Banks, 2015) and there is evidence of differential effects of viral genotypes in HIV-1-induced blood-brain barrier (BBB) inflammation (Bhargavan & Kanmogne, 2018; Woollard et al., 2014), we further assessed the effect of HIV genotypes on NP performance.

METHODS

Psychometric instruments

The 50-item PASAT (Diehr et al., 2003) [French version (Gronwall, 1977)] was used in this study, according to established procedures. Outcome measures included the number of responses attempted and the number of correct responses (range 0–49). The WMS-III Spatial Span subtest (Wechsler, 1997) was used to assess visuospatial (working) memory. The visual graphic memory test BVMT-R (R. Benedict, 1997) was used to assess visuospatial learning and delayed recall (memory) abilities, including short-term memory (immediate learning), long-term memory (delayed recall) and delayed recognition,

according to established procedures. For this study, total learning scores were used to assess visuospatial learning over the three trials, while delayed free recall scores were used to assess memory. The HVLT-R (Brandt, 2001) was used to assess verbal episodic memory, including immediate learning, delayed recall and recognition, according to established procedures. For this study, Total recall scores for trials-1 through 3 were used to assess verbal learning, while delayed recall scores were used to assess memory. We used the HVLT-R version previously translated into French, validated (Rieu et al., 2006) and pilot-tested in Cameroon (Kanmogne et al., 2010). The 12-item word list (in French) were: “lion, émeraude, cheval, tente, saphir, hôtel, cave, opale, tigre, perle, vache, hutte”. These words are commonly used in Cameroon (a majority French speaking country) and correspond respectively to the following English words: lion, emerald, horse, tent, sapphire, hotel, cave, opal, tiger, pearl, cow, and hut.

The PASAT-50, WMS-III Spatial Span, BVMT-R and HVLT-R were administered as part of a larger battery of 19 NP tests (Kanmogne et al., 2010), and co-normed to assess the specific domains of attention/WM, and visuospatial and verbal learning and memory function.

Adaptation of NP tests and study population

The NP tests and test instructions were translated into French, back-translated, standardized and pilot tested in Cameroon and quality assurance reviews were done on randomly selected data files as previously described (Kanmogne et al., 2010). These tests were part of a larger international battery (19 NP tests assessing 7 cognitive domains) that has been successfully used to detect HAND in developed and resource-limited countries, including countries in North America (Carey et al., 2004), South America (de Almeida et al., 2013), Asia (Cysique et al., 2007; Gupta et al., 2007), and in SSA (Akolo et al., 2014; Kabuba et al., 2017; Spies et al., 2012). Because combining normative data for all 19 tests with data and discussion regarding viral factors, ART, and immunological data, and their effects on neurocognitive performance, would be excessive for a single manuscript, this report focuses on attention/WM, learning, and memory (delayed recall). All study participants spoke French and all tests were administered in French. Subject recruitment, inclusion and exclusion criteria were done as previously described (Kanmogne et al., 2010) and are summarized in Table-1. We recruited a total of 742 subjects, including 395 healthy HIV− controls and 347 HIV+ subjects.

Ethical approval, data collection and norming procedure

This study was approved by the University of Nebraska Medical Center Institutional Review Board (IRB #307–06-FB) and the Cameroon National Ethics Committee (Ethical Clearance Authorization #146/CNE/SE/2012). Data was obtained in compliance with the Helsinki Declaration and written informed consent was obtained from all participants. After obtaining demographic information, the complete medical history of each subject was assessed, followed by a physical examination and a standardized neurological assessment to rule out any focal neurological deficit, CNS comorbidity and confound before psychometric testing. Attention/WM (PASAT-50 and WMS-III Spatial Span), learning and memory (HVLT-R and BVMT-R) tests were administered to each subject by trained psychometrists. Biological specimens were then collected for laboratory analyses. The procedures used for norming

were as previously described (Casaletto et al., 2015; Royston, 1994). Briefly, they involve converting raw scores into normalized scaled scores; developing regression-based formulas for calculation of T-scores that are corrected for demographic variables (age, gender and education); and calculation of deficit scores.

Laboratory analyses

Two different commercially available tests (rapid immunochromatographic HIV-1/2 test and the Murex HIV antigen/antibody Combination ELISA, Abbott Diagnostics, Chicago, IL, USA) were used per manufacturer's instructions to determine HIV serology. CD4 T-lymphocyte levels were quantified by flow cytometry and viral load (VL) by reverse transcription polymerase chain reaction (RT-PCR). Extraction of HIV RNA from patient's plasma, RT-PCR, amplification and sequencing of HIV genes [protease(PR), reverse transcriptase(RT), group specific antigen(gag), envelope (env,C2V3), transactivator of transcription(tat), and negative regulatory factor(nef)] were performed as previously described (Teto et al., 2017).

Statistical analyses

Student's *t*-tests (for continuous variables) and Fisher's exact test (for binary variables) were used for comparative analyses of cases and controls demographic data. Univariable analysis and simple linear regression were used to investigate associations of T-scores for attention/WM (PASAT-50 and WMS-III Spatial Span), learning (HVLT-R and BVMT-R Total Learning) and memory (HVLT-R and BVMT-R Delayed Recall) with demographic factors (age, gender, and education) in controls and cases. Linear regression models were used for analyses of T-scores and logistic regression models for analyses of impairment, and to compare the proportions with impairments in attention/WM, learning and memory between cases and controls: impaired if individual test deficit score≥1 and domain deficit score>0.5. Additional analyses of cases based on treatment status (untreated and on ART), CD4 counts (<350 and ≥350 cells/μl), VL (undetectable and detectable) and viral subtypes were performed. The R-software (v.3.5.0) was used for statistical analyses (significance threshold: $P<0.05$); Cohen's *d* effect sizes were used to assess differences in T-scores, Odds ratios and 95% confidence intervals (CI) were used to assess differences in proportions of impairment between the groups. P-values for individual tests were adjusted for multiple testing within each domain (k=2 for all) using false discovery rate (FDR) method. FDR was used to correct the P-values for analyses of the three domain scores (k=3). "Adj.P" are the P-values adjusted for multiple testing.

RESULTS

Demographic and laboratory characteristics

We recruited 742 subjects: 395 HIV− (controls, 34.7% males) and 347 HIV+ (cases, 22.2% males) (Table-1). Controls were 34.6±10.5 (mean ± standard deviation) years old (range 18–64), cases were 37.9±9.38 (range 18–60) years old. Controls had 12.4±4.23 (mean ± standard deviation) (range 0–20) years of education, cases had 9.65±3.78 (range 1–20) years of education. For cases, the median CD4 count was 407 cells/μl, 132 had detectable VL (mean logVL: 4.59±1.28 log copies/ml), 343 had known treatment status [189 (55.1%) on

ART, of whom 139 (73.5%) had undetectable VL; 148 (43.1%) treatment naïve, of whom 34 (23%) had undetectable VL (<50 copies/ml)].

Raw scores and standardized scores

Scaled scores and corresponding raw scores for PASAT-50 (number of correct responses) and WMS-III Spatial Span (total scores for Spatial Span: forward and backward), HVLT-R (total learning and delayed recall), and BVMT-R (total learning and delayed recall) are detailed in Table-2. The formulas used for regression-based analyses and calculation of T-scores (corrected for demographic variables) for attention/WM (PASAT-50 and WMS-III Spatial Span total scores), learning (HVLT-R and BVMT-R total learning), and memory (HVLT-R and BVMT-R delayed recall), are shown (Table-3). For both HIV− and HIV+ groups, analyses of raw scores showed effects of education (better performance on all tests by those with higher education), age (better performance on all tests by younger subjects), and gender (better performance by males on WMS-III Spatial Span (total scores), BVMT-R total learning, and BVMT-R delayed recall). Age and gender effects were absent in corrected T-scores of both HIV− and HIV+ samples; education effects were fully controlled on T-scores of controls and either fully controlled (HVLT-R and BVMT-R total learning and delayed recall; WMS-III Spatial Span total) or greatly attenuated (PASAT-50 and attention/WM summary score) in T-scores of cases.

HIV effects on attention/WM

Compared to controls, PLWH had significantly lower T-scores on PASAT-50 (P<0.001) but not on WMS-III Spatial Span total scores (P=0.3) (Table-4). However, PLWH had significantly lower attention/WM composite T-scores compared to controls (P=0.003, Adj.P=0.005, Table-4). Assessment of the extent of impairment showed that 23.1% of PLWH had impairment on PASAT-50, compared to 13.5% of controls (P=0.001, Adj.P=0.002, Table-5). Spatial Span data showed impairment among 17.5% of PLWH and 14% of controls (P=0.217), analysis of the composite domain deficit scores showed impairment in attention/WM in 17.5% of PLWH, compared to 12.7% of controls (P=0.087, Table-5).

HIV effects on learning

Compared to controls, T-scores of PLWH were significantly lower on the BVMT-R total recall (P=0.009, Adj.P=0.018), but not on the HVLT-R total recall (P=0.097) (Table-4). However, PLWH had significantly lower composite T-scores in the learning domain compared to controls (P=0.005, Table-4). Comparative analyses of the prevalence of impairments showed that 18.1 and 18.7% of PLWH had impairment on HVLT-R and BVMT-R total learning, compared respectively to 15.2% and 12.4% of controls; only impairment in BVMT-R total learning was significantly different (P=0.023, Adj.P=0.046, Table-5). Analysis of the composite learning domain deficit score showed learning impairment in 17% of PLWH, compared to 12.2% among controls (P=0.084, Adj.P=0.087, Table-5).

HIV effects on memory

PLWH had significantly lower T-scores on HVLT-R delayed recall (P=0.013, Adj.P=0.021) and BVMT-R delayed recall (P=0.021), as well as memory composite T-scores (P=0.002, Adj.P=0.005), compared to controls (Table-4). Analyses of the prevalence of impairments showed that among PLWH, 21.5 and 21.2% had impairment on HVLT-R and BVMT-R delayed recall, compared respectively to 12.7% (P=0.002, Adj.P=0.004) and 15.1% (P=0.04) among controls (Table-5). Analysis of the composite memory domain deficit score showed that the proportion of PLWH with impairment in memory (20.6%) was significantly higher than the proportion seen in controls (12.7%) (P=0.006, Adj.P=0.018, Table-5).

Effects of VL and antiretroviral treatment on attention/WM, learning, and memory

To assess viremia and treatment effects on attention/WM, learning, or memory, we compared T-scores of PLWH who had undetectable and detectable VL, on treatment or not. No significant differences were found between those who were virally suppressed and those with detectable viremia; or those on ART and no-ART on attention/WM, learning, or memory (Table-6). To determine whether ART could influence any interaction of viremia and cognitive function, we performed separate analyses of cases on ART and no-ART group. For cases on ART, those with undetectable (n=128) and detectable (n=36) VL showed no group differences in attention/WM (PASAT-50: *d*: −0.17; 95% CI: −0.55, 0.2; P=0.36, Adj.P=0.44; Spatial Span: *d*: −0.15; 95% CI: −0.52, 0.23; P=0.44; composite attention/WM T-scores: *d*: −0.2; 95% CI: −0.57, 0.17; P=0.288, Adj.P=0.479), learning (HVLT-R total learning: *d*: −0.01; 95% CI: −0.39, 0.36; P=0.937; BVMT-R total learning: *d*: 0.2; 95% CI: −0.18, 0.57; P=0.3, Adj.P=0.6; composite learning T-scores: *d*: 0.12; 95% CI: −0.25, 0.49; P=0.526), or memory (HVLT-R delayed recall: *d*: 0.18; 95% CI: −0.2, 0.55; P=0.349, Adj.P=0.528; BVMT-R delayed recall: *d*: 0.12; 95% CI: −0.25, 0.49; P=0.528; composite memory T-scores: *d*: 0.19; 95% CI: −0.18, 0.56; P=0.32, Adj.P=0.479).

For no-ART cases, those with undetectable (n=38) and detectable (n=89) VL showed no group differences in attention/WM T-scores (PASAT-50: *d*: −0.02; 95% CI: −0.41, 0.36; P=0.91; Spatial Span: *d*: 0.21; 95% CI: −0.17, 0.6; P=0.261, Adj.P=0.522; composite attention/WM T-scores: *d*: 0.14; 95% CI: −0.25, 0.53; P=0.493). Analysis of learning data for no-ART cases showed significantly lower BVMT-R total learning T-scores for those with undetectable VL, compared to those with detectable VL (*d*: 0.4; 95% CI: 0.01, 0.79; P=0.037). However, this statistical significance diminished when analyses were corrected for individual learning tests (Adj.P=0.074). There was no difference in HVLT-R total learning T-scores (*d*: −0.08; 95% CI: −0.47, 0.3; P=0.666), or overall learning T-scores (*d*: 0.2; 95% CI: −0.19, 0.58; P=0.298, Adj.P=0.447) of non-treated cases with undetectable VL and those with detectable VL.

Analysis of memory data of untreated cases showed no significant difference in HVLT-R delayed recall T-scores of those with undetectable VL, compared to those with detectable VL (*d*: 0.22; 95% CI: −0.16, 0.61; P=0.232). However, untreated cases with undetectable VL had significantly lower BVMT-R delayed recall T-scores (*d*: 0.41; 95% CI: 0.02, 0.8; P=0.029, Adj.P=0.058), and lower overall memory summary T-scores (*d*: 0.4; 95% CI: 0.01, 0.78; P=0.039), compared to untreated cases with detectable viremia. Despite the high effect

size, the statistical significance diminished when analyses were corrected for individual memory tests (Adj.P=0.117).

Further analyses of PLWH who had undetectable VL (n=165), 50>VL<100,000 copies/ml (n=76), and VL ≥100,000 copies/ml (n=49), untreated or on ART, showed no differences in attention/WM T-scores or composite scores between the groups (P values: 0.34–0.97). Analysis of learning scores showed that PLWH who had very high VL (≥100,000 copies/ml) had lower HVLT-R total learning T-scores, compared to those with lower or undetectable VL (P=0.043, Adj.P=0.086); but there was no difference in BVMT-R total learning (P=0.669) or learning summary scores (P=0.542, Ajd.P=0.8) between the groups. Similarly, there was no difference in individual memory T-scores or the overall memory composite scores (P =0.826) between the groups.

Effects of current immune status and viral subtype on attention/WM, learning, and memory

Comparative analyses of T-scores of PLWH who had low (<350 cells/μl) and higher (≥350 cells/μl) CD4 counts showed no significant differences between those with low and higher CD4 count on attention/WM, learning, or memory (Table-6). Analyses of the viral PR, RT, gag, env, tat, and nef sequences showed a high genetic diversity (Acharya et al., 2019; Kanmogne et al., 2018; Teto et al., 2016; Teto et al., 2017). These patients were predominantly infected with HIV-1 CRF02_AG (AG) (59–71.6%), but there were also individuals infected with non-CRF02_AG viruses (non-AG) or viruses that had CRF02_AG genotype in some of the six gene regions analyzed and different genotypes in other gene regions (AG-Plus). To investigate whether HIV subtype influence the individual's attention/WM, learning, or memory, we analyzed T-scores of cases infected with AG (58.17%) and those infected with non-AG (26.8%) or AG-Plus (15.03%) viruses. Attention/WM data showed a small effect of viral genotype on individual T-scores on PASAT-50 (*d*: 0.23) and Spatial Span total (*d*: 0.27) T-scores when comparing cases infected with AG and those infected with non-AG and AG-Plus viruses (Table-6). Analyses of the composite attention/WM T-scores showed that compared to cases infected with AG viruses, those infected with non-AG and AG-Plus viruses had significantly lower (worse) overall attention/WM T-scores (*d*: 0.35; 95% CI: 0.02, 0.68; P=0.038); this statistical significance diminished when analyses were corrected for individual attention/WM tests (Adj.P=0.114). There was no significant difference in HVLT-R and BVMT-R total learning T-scores or the overall learning composite T-scores of cases infected with AG and those infected with non-AG and AG-Plus viruses (Table-6). Similarly, there was no significant difference in HVLT-R and BVMT-R delayed recall or the overall memory composite T-scores of cases infected with AG and those infected with non-AG and AG-Plus viruses (Table-6).

DISCUSSION

Valid assessment of human cognitive abilities and accurate diagnosis of acquired neurocognitive disorders requires population-appropriate, demographically-corrected normative standards, because performances on neurocognitive tests are influenced by population socio-demographic factors, language and cultural backgrounds (Casaletto et al., 2015; Saloner & Cysique, 2017). The current study reports the first adult normative data

for assessing attention/WM, learning and memory in Cameroon and provides normative standards corrected for demographic factors, based on results of healthy HIV-seronegative controls for two validated tests of attention/WM and two validated tests of learning and memory. Comparative analyses of controls and cases using demographically-corrected T-scores showed significant HIV effects on attention/WM, learning and memory.

The tests used to assess attention/WM in this study included PASAT-50 and WMS-III Spatial Span. PASAT has been used to detect impairment in attention/WM among individuals with several conditions affecting the CNS, including multiple sclerosis (Kujala et al., 1995), Parkinson's disease (Dujardin et al., 2007), epilepsy (Prevey et al., 1998), traumatic brain injury (O'Jile et al., 2006), and HAND (Cysique et al., 2014; Kabuba et al., 2017). The Spatial Span sub-test of the WMS-III assesses an individual's ability to pay attention to information, to hold and process that information, and to formulate a response based on that information (Wechsler, 1997). In our current study, the Spatial Span individually was not sensitive in differentiating HIV+ persons from seronegative controls. However, the PASAT-50 and overall attention/WM summary scores showed significantly lower T-scores for cases and significantly higher proportion of cases with impairment in attention/WM, compared to controls.

Tests of episodic memory assess a person's ability to encode, store and retrieve information and correlate with function of the brain systems involving frontotemporal regions (Cowan, 2008; Wilde et al., 2004). The tests used to assess learning and episodic memory in this study included BVMT-R and HVLT-R. The BVMT-R assesses visuospatial learning, retention, and overall episodic memory abilities (R. Benedict, 1997) and is sensitive in detecting impairments of visuospatial episodic memory abilities in individuals with multiple sclerosis (R. H. Benedict & Zivadinov, 2007), Parkinson's disease (Foster et al., 2010), traumatic brain injuries (Belanger et al., 2009) and HAND (Cysique et al., 2014; Heaton et al., 2010; Kabuba et al., 2017). The HVLT-R assesses verbal learning, retention and overall episodic memory abilities; it has been shown to be sensitive in detecting impairments of verbal episodic memory in humans with HIV/AIDS across different cross-cultural settings, in both developed and resources-limited countries (Heaton et al., 2010; K. Robertson et al., 2016). Each of the four individual measures of learning and memory showed some HIV effects and contributed to a stronger HIV effect on the summary scores. Of the two measures of attention/WM, PASAT-50 showed HIV effects and drove the overall attention/WM summary scores. The Spatial Span showed no HIV effect contrary to findings in other SSA countries (Hestad et al., 2019) where Spatial Span demonstrated robust sensitivity to HIV. These discrepancies could be due to differences between the two populations, including differences in language, culture, healthcare and education systems.

The effect sizes for individual NP tests and domain T-scores in our studies are in the same ranges as effect sizes observed in some large US cohort studies (Maki et al., 2015; Rubin et al., 2015). The proportion of cases in this study with impairment based on individual tests or domain T-scores (17–23%) is in line with our previous findings (Kanmogne et al., 2018; Kanmogne et al., 2010; Njamnshi et al., 2009; Njamnshi et al., 2008) and some previously reported prevalence of HAND in Nigeria (21.5%) (Yusuf et al., 2017) and South Africa (23%) (Joska et al., 2010). However, these are much lower than HAND prevalence reported

among HIV-infected adults in other studies in Nigeria, China, and India (26–28%) (Jumare et al., 2019; Royal et al., 2012); South Africa (36–53%) (Joska et al., 2011; Mogambery et al., 2017), Botswana (37–38%) (Lawler et al., 2011), Zambia (34–35%) (Kabuba et al., 2017), Uganda (38–64%) (Nakku et al., 2013; Sacktor et al., 2019; Yechoor et al., 2016), and the United States (36–45%) (Heaton et al., 2015). Test instruments used in these studies varied from simpler International HIV Dementia Scale to more complete NP batteries, and such differences could have played a role in the wide variations in HAND prevalence observed across studies. The lower rates of NCI observed in our study could also be due to the limited number of NP tests used. Our forthcoming report on the global deficit score from the entire battery [19 NP tests assessing 7 cognitive domains] will give a more conclusive estimate of the rate of HAND in Cameroon.

Previous studies in developed (Rubin et al., 2017; Woods et al., 2005) and resource-limited settings (Akolo et al., 2014; Kabuba et al., 2017; Lawler et al., 2011) also showed increased impairment in attention/WM, learning, and memory in PLWH. These HIV-induced NCI often have other functional and behavioral implications, including for activities of daily living and medication adherence. In fact, studies of PLWH have shown a link between cognitive performance and ART adherence, with impairments in attention/WM, verbal learning and memory associated with poor adherence; and higher adherence was predictive of improved cognition, including improvement in attention and executive function (Ettenhofer et al., 2010; Obermeit et al., 2015).

The mechanisms of HIV-induced impairments in attention/WM, learning and memory have not been elucidated. Combined cognitive assessment (using HVLT-R, BVMT-R) and magnetic resonance imaging (MRI) (Wang et al., 2015) or functional MRI (Cohen et al., 2018) of PLWH showed significantly decreased performance in verbal learning and memory among PLWH, with a positive correlation between increased hippocampal N-acetylaspartate/creatinine levels and performance in HVLT-R and BVMT-R (Wang et al., 2015). These MRI studies also showed differences in association between the degree of NCI and brain conductive function and metabolic changes based on brain regions (Wang et al., 2015). Functional MRI also showed that functional brain response predicted neurocognitive outcomes, as reduced neural activation among HIV+ adults predicted deficits in attention and working memory (Cohen et al., 2018). Studies of post-mortem brain tissues found significant decrease in dopamine levels in the substantia nigra of PLWH, with a correlation between decreased dopamine levels and poor T-scores in NP tests, including tests of learning, speed of information processing and memory (Kumar et al., 2011). This suggest that decreased dopamine levels in the substantia nigra directly correlate with poor neurocognitive performance.

In the current study, viremia influenced learning and memory function among untreated cases. The natural history of HIV infection is characterized by higher VL in the earlier phases of infection, but viremia drops as the immune response develops and the subsequent prolonged period of clinical latency and asymptomatic infection is characterized by lower VL (Mindel & Tenant-Flowers, 2001; Sabin & Lundgren, 2013). Therefore, although we do not know the exact duration of infection of our cases, it is likely that untreated cases in our study who had higher/detectable VL may have been more recently infected, whereas

untreated cases who had undetectable VL may have been in the chronic/clinical latency phase and had been infected for a much longer period, thus with increased susceptibility of developing HAND. This hypothesis is further supported by the fact the Cameroon hospitals where most of our cases were recruited had adopted the recommended WHO policy of offering ART to individuals as soon as they are diagnosed with HIV infection; and most of untreated cases in our study were newly diagnosed cases. Thus, we recruited and administered NP tests, assessed VL and CD4+ T-cells levels of these individuals before ART initiation.

There have been reports of a small percentage (1.7–6.3%) of treatment-naïve PLWH with viral suppression (Erb et al., 2000; Martinson et al., 2014). Studies of ART-naïve PLWH in India (Haokip, 2018), Nigeria (Odaibo et al., 2013) and Spain (Garcia et al., 1997) also showed undetectable VL in 8.5%, 9.5%, and 16% of subjects respectively. Our current study population showed a much higher percentage (23%) of no-ART cases with undetectable VL. The reasons for such unusually higher proportion of virally suppressed treatment-naïve cases are unclear. In a British seroprevalence survey, some subjects considered newly diagnosed that had undetectable VL also tested positive for antiretrovirals (ARVs) drugs (Sullivan et al., 2013). In clinical trials enrolling newly diagnosed HIV+ individuals, retrospective analysis of blood samples collected at enrolment showed ARVs drugs in 46%−78% of samples from subjects with low or undetectable VL who had reported no prior knowledge of their HIV status and no prior exposure to ART (Fogel et al., 2013; Kahle et al., 2014; Marzinke et al., 2014). However, it is unlikely that treatment-naïve cases in our study were on ART and misreported their status. There was no incentive in our study to enroll as treatment-naïve; we enrolled both naïve and subjects on ART, and most treatment-naïve subjects were enrolled at hospitals HIV testing and counselling centers where they were undergoing the required counselling before ART initiation. Provision of ARVs drugs and monthly treatment follow-up also occur at the same hospital centers. It is possible that other factors such as use of medicinal plants could have contributed to the high proportions of no-ART subjects with viral suppression. In fact, there is evidence that some medicinal plants extracts, including natural plants from Cameroon and other African countries, have anti-viral activity and can inhibit cellular infection and HIV replication (Ayisi & Nyadedzor, 2003; Helfer et al., 2014; Leteane et al., 2012; Mbaveng et al., 2011; Tietjen et al., 2015). Medicinal plants and plants-based substances from traditional healers are widely used by Cameroonians for various illnesses, and a recent survey showed that 55% of HIV-infected Cameroonians were regularly using medicinal plants (Mabou Tagne et al., 2019). This could have contributed to the smaller HIV effects observed in our study. Unfortunately, most people taking herbal medicine and other substances from traditional healers do not disclose such information to health care providers (Haile et al., 2017), and we don’t know who among our subjects may have been taking herbal medicine. Our data showing increased neurocognitive deficits in untreated cases with viral suppression underscore the discordance between standard disease indices and risk of NCI.

Our data showing no effect of ART or current CD4 T-cells levels on attention/WM, learning, or memory, agree with other studies showing that HAND persists in the ART era, with no major effect of VL, ART use or current CD4 T-cells levels on cognitive function. In fact, a 3-year longitudinal study of young adults starting ART found no major effect of ART

on attention/WM, learning, or memory (Nichols et al., 2016). A recent 4-year longitudinal study of PLWH on ART and virologically suppressed, found that NCI persisted and there were no significant differences in the proportion with NCI at baseline and at 4-years (K. Robertson et al., 2018). Several other studies in SSA including in Nigeria (Akolo et al., 2014; Salawu et al., 2008), Uganda (K. R. Robertson, Nakasujja, et al., 2007), Botswana (Lawler et al., 2011) and Zambia (Kabuba et al., 2017) found that compared to seronegative controls, PLWH had significant deficits in attention/WM, learning and memory, but there was no significant association between NP test scores and blood CD4 counts (Akolo et al., 2014; Lawler et al., 2010; Salawu et al., 2008). Studies in Europe and USA have also shown significantly lower performance in tests of attention/WM, learning and memory in PLWH, but no significant association between cognitive performance and CD4 counts, VL, duration of ART use, or drugs CNS penetration scores (Malagurski et al., 2018; Rubin et al., 2017). There is evidence that low nadir CD4 counts predict NCI (Ellis et al., 2011; Valcour et al., 2006), but we did not have nadir CD4 values, and used the CD4 counts at enrolment in our current studies.

Inflammation plays a major role in HAND pathogenesis; HIV-1 virions and viral proteins induce expression of inflammatory cytokines and chemokines in brain cells *in vitro* and *in vivo* (Hong & Banks, 2015; Yang et al., 2009). The role of viral subtypes in HIV-induced inflammation and HAND is not clear. Long-term (3–9.5 years) follow-up of PLWH showed significantly reduced viral fitness, virulence, slower rates of CD4+ T-cells decline and disease progression among clade-C infected subjects, compared to subjects infected with clade-A or D (Venner et al., 2016). Comparative studies of clades B and C showed mixed results. Some studies showed that compared to clade-B viruses and Tat-B proteins, HIV-1 clade-C and Tat-C induced less cellular inflammation (Gandhi et al., 2009; Kennedy et al., 2014; Yndart et al., 2015), and were less neurovirulent, resulting in lower incidence of HAND (Rao et al., 2008; Satishchandra et al., 2000); and that C31S substitution in Tat-C played a role in these differential inflammation and neurovirulence (Ranga et al., 2004; Rao et al., 2013). However other studies showed that HAND is prevalent among clade-C-infected subjects (Gupta et al., 2007; Kamat et al., 2017; Tilghman et al., 2014). Studies of demographically similar PLWH showed similar decline in imaging markers of brain integrity (Hoare et al., 2011; Ortega et al., 2013; Paul et al., 2017), similar levels of inflammatory cytokines and chemokines in serum and cerebrospinal fluids (de Almeida et al., 2016), and similar rates of HAND (de Almeida et al., 2013) between clade-B and clade-C infected subjects, independent of Tat C31S substitution (Paul et al., 2017). It is not known if viral subtype could influence HAND severity, as some studies that showed similar overall HAND prevalence between these clades also showed 3-fold higher prevalence of HIV-associated dementia among clade-B (15%) compared to clade-C (5%) infected subjects (de Almeida et al., 2013).

There is also evidence of differential BBB inflammation with clades B and AG viruses, with significantly lower levels of inflammatory cytokines and chemokines in BBB cells exposed to CRF02_AG Tat proteins, compared to cells exposed to subtype-B Tat (Bhargavan & Kanmogne, 2018; Woollard et al., 2014). CRF02_AG is the predominant subtype in West-Central Africa, including in Cameroon (Brennan et al., 2008), and 67–72% of cases in our study harbored CRF02_AG viruses (Teto et al., 2016; Teto et al., 2017). Because of

this differential inflammation with CRF02_AG viruses and increased risk of NCI associated with CNS inflammation in PLWH, we investigated whether viral genotype had differential effects on attention/WM, learning, and memory. Data showed no difference in learning or memory based on HIV genotype but compared to subjects infected with AG-Plus and non-AG HIV-1, subjects infected with AG viruses had higher functioning on the overall composite attention/WM T-scores. Therefore, previous findings of reduced inflammation with AG viruses and Tat.AG (Bhargavan & Kanmogne, 2018; Woollard et al., 2014) may be associated with less impairment in executive function (Kanmogne et al., 2018) and reduced deficits in attention/WM among subjects harboring AG viruses, compared to subjects infected with other HIV genotypes. Our subsequent studies will determine whether there is a correlation between viral genotype, systemic inflammation and risk of other NCIs in these subjects. Comparative neurocognitive studies of subjects infected with HIV-1 subtype G and CRF02_AG in Nigeria also showed significantly lower mean global T-scores and 2.2-times higher odds of NCI with subtype-G infection, compared to AG-infected subjects (Jumare et al., 2017). *In vivo* studies also showed slower decline in CD4+ T-cells and weight in animals infected with AG viruses compared to animals infected with HIV-1 clade-B (Bhargavan & Kanmogne, 2019). The reduced inflammation, less NCI, less cytopathicity and less destruction of immune cells observed with AG-viruses likely contributed to a better adaptation, transmission and expansion of this clade throughout West and Central Africa.

Potential limitations of this study include some differences in gender, education, and age between cases and controls. However, use of test scores corrected for demographic variables fully controlled or highly mitigated these differences. Socio-economic status can influence performance on NP tests (Arentoft et al., 2015) but we do not know the socio-economic status of recruited subjects, or whether such unmeasured background differences could have influenced the results. Most subjects were recruited from Yaoundé and nearby suburban neighborhoods. These potential limitations however, are mitigated by the fact that Yaoundé (largest city in Cameroon with >3 million inhabitants) includes people from diverse backgrounds and from all Cameroonian ethnic groups (IndexMundi, 2018).

In conclusion, analyses of demographically-corrected scores showed that PLWH in Cameroon had significantly lower composite attention/WM, learning and memory T-scores; and a higher proportion had impairments in attention/WM, learning and memory, compared to controls. Infection with non-AG and AG-Plus subtypes was associated with increased deficits in attention/WM, compared to PLWH infected with AG viruses. Cross-sectional analyses showed no association between T-scores and ART or CD4 counts. However, among untreated PLWH, undetectable VL was associated with impairment in learning and memory. This may correspond to a longer duration of HIV infection among this group. This study provides adult normative standards for two NP tests of attention/WM (PASAT-50 and WMS-III Spatial Span) and two tests of learning and memory (BVMT-R and HVLT-R). These reference values will facilitate future studies of attention/WM, learning and memory in Cameroon and studies of diseases affecting the cognitive functioning of Cameroonians.

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Table 1:

Demographic and clinical characteristics by HIV status. Values are Mean (SD), Median [IQR], or N (%).

Characteristics	HIV−		HIV+		P Value
	N[a]	Mean (SD) or N (%)	N[a]	Mean (SD), Median [IQR], or N (%)	
DEMOGRAPHICS					
Age (years)	395	34.6 (10.5)	347	37.9 (9.38)	<0.001
Age range [IQR] (years)		18 – 64 [26, 42]		18 – 60 [31, 45]	
Education (years)	394	12.4 (4.23)	346	9.65 (3.78)	<0.001
Education range [IQR] (years)		0 – 21 [9, 16]		1 – 20 [6, 12]	
Male, N (%)	395	137 (34.7%)	347	77 (22.2%)	<0.001
HIV DISEASE					
CD4	-	-	306	407 [246, 574]	-
Viral Load, N (%)			305		
- Undetectable				173 (56.7%)	
- Detectable				132 (43.3%)	
Log10 Viral Load (among subjects with detectable VL)	-	-	132	4.59 (1.28)	-
HIV-1 CRF02_AG subtypes				58.17%	
Non-CRF02_AG subtypes				41.83%	
ART Status, N (%)			343		
- ART	-	-	-	189 (55.1%)	-
- Naive	-	-	-	148 (43.1%)	-
- Not Current	-	-	-	5 (1.46%)	-

Notes: Student's t-test was applied for continuous variables, and Fisher's exact test for categorical variables; SD, standard deviation; IQR, interquartile range.

[a]Total number of participants with available data for the corresponding variable.

Subjects recruitment sites: HIV+ cases were recruited from 1) the HIV voluntary counseling and testing sections of the Day-care Service in the Yaoundé Central Hospital; 2) the Yaoundé Jamot Hospital; 3) the Efoulan District Hospital, Yaoundé; and 4) the Etoug-Ebe Baptist Hospital, Yaoundé. Seronegative controls were recruited from the same health services, as well as among 1) caregivers and visitors to the Neurology outpatient clinic and Day-care service in the Yaoundé Central Hospital; 2) the Health and Social Welfare Centre of the University of Yaoundé-1; and 3) Yaoundé general population.

Exclusion criteria: 1) present or past history of CNS disease unrelated to HIV, 2) head trauma, 3) current alcohol intoxication (blood alcohol content of each participant was measured using a Breathalyzer), 4) known psychiatric disease or treatment with antipsychotic drugs, and 5) ongoing systemic illness or fever (temperature of 37.5°C or higher).

Inclusion criteria: adults at least 18 years old with no exclusion criteria and able to give a written consent.

Table 2:

Conversion of the raw scores to scaled scores for tests assessing attention/WM, learning and memory domains.

	Attention/WM		Learning		Memory		
Scaled Score	**PASAT Correct**	**Spatial Span Total**	**HVLT-R Total Recall**	**BVMT-R Total Recall**	**HVLT-R Delayed Recall**	**BVMT-R Delayed Recall**	**Scaled Score**
1	-	0–4	0–7	-	0	-	**1**
2	-	5	8–9	0	1	0	**2**
3	0	6	10	1–2	2	-	**3**
4	1–5	7	11–12	3	-	1–2	**4**
5	6–8	8	13	4–6	3	3	**5**
6	9–11	9	14–15	7–10	4	4	**6**
7	12–13	10	16–17	11–14	-	5–6	**7**
8	14–16	11	18–19	15–19	5	7–8	**8**
9	17–19	12	20	20–22	6	9	**9**
10	20–21	13	21–22	23–24	7	10	**10**
11	22–24	14	23–24	25–27	8	11	**11**
12	25–29	15–16	25–26	28–29	9	-	**12**
13	30–33	17	27	30	-	12	**13**
14	34–37	18	28–29	31–32	10	-	**14**
15	38–40	19	30	33–34	11	-	**15**
16	41–42	20	31	35	-	-	**16**
17	43–44	21–23	32	36	12	-	**17**
18	45–48	24–27	33–34	-	-	-	**18**
19	49	28–32	35–36	-	-	-	**19**

Table 3.

T-score calculation formulas based on scaled scores for tests assessing attention/WM, learning and memory domains.

Test	Formula
Attention/WM Domain	
PASAT-R Correct	50 + 10*[(scaled score) – (7.9122 + 2.4260*((edu + 1)/10) – 3.5543*(age/100) + 0.0713*male)]/2.7261
Spatial Span Total	50 + 10*[(scaled score) – (7.4951 + 2.8769*((edu + 1)/10) – 4.9839*(age/100) + 0.6297*male)]/2.7489
Learning Domain	
HVLT-R Total Recall	50 + 10*[(scaled score) – (7.6307 + 5.2578*((edu + 1)/10)^2 – 1.9497*((edu + 1)/10)^3 – 5.7325*(age/100) + 0.0336*male)]/2.4772
BVMT-R Total Recall	50 + 10*[(scaled score) – (7.5089 + 2.9896*((edu + 1)/10) – 4.9868*(age/100) + 0.5772*male)]/2.6067
Memory Domain	
HVLT-R Delayed Recall	50 + 10*[(scaled score) – (7.8029 + 3.0362*((edu + 1)/10) – 5.0123*(age/100) – 0.5062*male)]/2.6146
BVMT-R Delayed Recall	50 + 10*[(scaled score) – (7.7140 + 2.7984*((edu + 1)/10) – 5.2135*(age/100) + 0.4162*male)]/2.4451

Abbreviation: edu = education; male = 1 for male, 0 for female.

Table 4.

Comparisons of attention/WM, learning, and memory demographically-corrected T-scores between controls and HIV+ patients.

Test	HIV- (N=395)		HIV+ (N=347)		Cohen's d (95% CI)	P Value	Adj. P Value
	N	Mean (SD)	N	Mean (SD)			
Attention/WM Domain							
PASAT Correct	362	50.0 (10.0)	316	47.2 (9.77)	−0.29 (−0.44, −0.14)	<0.001	<0.001
Spatial Span Total	363	50.0 (10.0)	320	49.2 (10.2)	−0.08 (−0.23, 0.07)	0.302	0.302
Attention Summary Score	361	50.0 (7.92)	315	48.2 (8.02)	−0.23 (−0.38, −0.08)	0.003	0.005
Learning Domain							
HVLT-R Total Recall	363	50.0 (9.99)	321	48.7 (10.6)	−0.13 (−0.28, 0.02)	0.097	0.097
BVMT-R Total Recall	363	50.0 (10.0)	321	47.9 (10.4)	−0.20 (−0.35, −0.05)	0.009	0.018
Learning Summary Score	362	50.1 (7.78)	321	48.3 (8.43)	−0.22 (−0.37, −0.06)	0.005	0.005
Memory Domain							
HVLT-R Delayed Recall	363	50.0 (10.0)	321	48.0 (10.8)	−0.19 (−0.34, −0.04)	0.013	0.021
BVMT-R Delayed Recall	364	50.0 (9.99)	321	48.1 (11.2)	−0.18 (−0.33, −0.03)	0.021	0.021
Memory Summary Score	363	50.1 (7.99)	321	48.1 (8.88)	−0.24 (−0.39, −0.09)	0.002	0.005

Notes: Cohen's d compares HIV+ to HIV−; the higher the T-score, the better NP performance is. SD, standard deviation; CI, confidence interval; HVLT, Hopkins verbal learning test; BVMT, brief visuospatial memory test. Adj, adjusted. Adjusted P values were corrected for individual tests within each domain; and p-values for domain summary scores were adjusted for all comparisons. Adjustments were done using the false discovery rate (FDR) method.

Table 5.

Comparisons of proportions of impairment in attention/WM, learning, and memory domains between controls and HIV+ patients.

Test	HIV− (N=395)		HIV+ (N=347)		OR (95% CI)	P Value	Adj. P Value
	N	N impaired (%)	N	N impaired (%)			
Attention Domain							
PASAT Correct	362	49 (13.5%)	316	73 (23.1%)	1.92 (1.29, 2.86)	0.001	0.002
Spatial Span Total	363	51 (14.0%)	320	56 (17.5%)	1.30 (0.86, 1.96)	0.217	0.217
Attention Summary Domain	361	46 (12.7%)	315	55 (17.5%)	1.45 (0.95, 2.21)	0.087	0.087
Learning Domain							
HVLT-R Total Recall	363	55 (15.2%)	321	58 (18.1%)	1.23 (0.82, 1.85)	0.306	0.306
BVMT-R Total Recall	363	45 (12.4%)	321	60 (18.7%)	1.62 (1.07, 2.47)	0.023	0.046
Learning Summary Domain	362	44 (12.2%)	321	54 (16.8%)	1.46 (0.95, 2.25)	0.084	0.087
Memory Domain							
HVLT-R Delayed Recall	363	46 (12.7%)	321	69 (21.5%)	1.89 (1.25, 2.84)	0.002	0.004
BVMT-R Delayed Recall	364	55 (15.1%)	321	68 (21.2%)	1.51 (1.02, 2.24)	0.040	0.040
Memory Summary Domain	363	46 (12.7%)	321	66 (20.6%)	1.78 (1.18, 2.69)	0.006	0.018

Notes: OR, odds ratio, compares HIV+ to HIV−. CI, confidence interval; HVLT, Hopkins verbal learning test; BVMT, brief visuospatial memory test. Impaired, domain deficit score>0.5 or individual test deficit score>=1. Adj, adjusted. Adjusted P values were corrected for individual tests within each domain; and p-values for domain summary scores were adjusted for all comparisons. Adjustments were done using the false discovery rate (FDR) method.

Table 6

Comparisons of attention/WM, learning, and memory demographically-corrected T-scores between HIV+ patients based on viral loads, ART use, immune status, and viral genotype.

EFFECTS OF VIRAL LOADS							
Test	**VL undetectable**		**VL detectable**		**Cohen's d (95% CI)**	**P Value**	**Adj. P Value**
	N	**Mean (SD)**	**N**	**Mean (SD)**			
Attention/WM Domain							
PASAT Correct	164	47.4 (9.49)	124	47.3 (10.6)	0.00 (−0.23, 0.24)	0.970	0.97
Spatial Span Total	166	48.6 (9.92)	124	50.1 (10.9)	−0.15 (−0.38, 0.09)	0.212	0.424
Attention Summary Score	164	48.0 (7.77)	123	48.8 (8.79)	−0.10 (−0.34, 0.13)	0.401	0.76
Learning Domain							
HVLT-R Total Recall	166	49.7 (10.4)	125	48.4 (10.8)	0.12 (−0.12, 0.35)	0.323	0.353
BVMT-R Total Recall	166	47.5 (10.2)	125	48.6 (10.4)	−0.11 (−0.34, 0.12)	0.353	0.353
Learning Summary Score	166	48.6 (8.31)	125	48.5 (8.37)	0.01 (−0.23, 0.24)	0.964	0.964
Memory Domain							
HVLT-R Delayed Recall	166	48.2 (10.4)	125	48.5 (10.7)	−0.03 (−0.27, 0.20)	0.782	0.782
BVMT-R Delayed Recall	166	47.6 (11.2)	125	48.7 (11.1)	−0.09 (−0.33, 0.14)	0.426	0.78
Memory Summary Score	166	47.9 (8.25)	125	48.6 (9.16)	−0.08 (−0.31, 0.15)	0.508	0.76

EFFECTS OF ART							
Test	**No ART**		**On ART**		**Cohen's d (95% CI)**	**P Value**	**Adj. P Value**
	N	Mean (SD)	N	Mean (SD)			
Attention/WM Domain							
PASAT Correct	142	46.3 (9.66)	170	47.8 (9.93)	−0.15 (−0.37, 0.08)	0.202	0.404
Spatial Span Total	145	49.3 (11.1)	171	49.1 (9.41)	0.02 (−0.20, 0.24)	0.879	0.879
Attention Summary Score	141	47.8 (8.31)	170	48.4 (7.88)	−0.07 (−0.30, 0.15)	0.523	0.785
Learning Domain							
HVLT-R Total Recall	146	47.7 (11.2)	171	49.7 (10.2)	−0.19 (−0.41, 0.03)	0.096	0.192
BVMT-R Total Recall	146	48.0 (11.2)	171	47.7 (9.68)	0.03 (−0.19, 0.26)	0.780	0.780
Learning Summary Score	146	47.8 (9.05)	171	48.6 (7.92)	−0.10 (−0.32, 0.13)	0.397	0.785
Memory Domain							
HVLT-R Delayed Recall	146	48.3 (11.1)	171	47.9 (10.6)	0.03 (−0.19, 0.26)	0.759	0.759
BVMT-R Delayed Recall	146	47.7 (11.9)	171	48.4 (10.6)	−0.06 (−0.28, 0.16)	0.603	0.759
Memory Summary Score	146	48.0 (9.56)	171	48.1 (8.32)	−0.02 (−0.24, 0.21)	0.884	0.884

EFFECTS OF CD4 COUNTS							
Test	**CD4 <350 cells/μl**		**CD4 ≥350 cells/μl**		**Cohen's d (95% CI)**	**P Value**	**Adj. P Value**
	N	Mean (SD)	N	Mean (SD)			
Attention/WM Domain							
PASAT Correct	116	47.1 (9.97)	171	47.4 (9.96)	0.02 (−0.21, 0.26)	0.844	0.927
Spatial Span Total	115	49.3 (10.9)	174	49.1 (9.92)	−0.01 (−0.25, 0.23)	0.927	0.927

EFFECTS OF VIRAL LOADS

Test	VL undetectable		VL detectable		Cohen's d (95% CI)	P Value	Adj. P Value
	N	Mean (SD)	N	Mean (SD)			
Attention Summary Score	115	48.2 (8.64)	171	48.3 (7.85)	0.01 (−0.23, 0.25)	0.949	0.949
Learning Domain							
HVLT-R Total Recall	116	48.9 (11.6)	174	49.2 (9.60)	0.03 (−0.21, 0.27)	0.804	0.804
BMVT-R Total Recall	116	47.4 (10.4)	174	48.1 (10.2)	0.07 (−0.17, 0.30)	0.588	0.804
Learning Summary Score	116	48.1 (9.24)	174	48.6 (7.54)	0.05 (−0.18, 0.29)	0.626	0.949
Memory Domain							
HVLT-R Delayed Recall	116	48.5 (11.1)	174	48.1 (10.0)	−0.03 (−0.27, 0.20)	0.791	0.791
BVMT-R Delayed Recall	116	48.4 (11.2)	174	47.8 (11.2)	−0.05 (−0.29, 0.19)	0.680	0.791
Memory Summary Score	116	48.4 (9.22)	174	48.0 (8.26)	−0.05 (−0.28, 0.19)	0.698	0.949

EFFECTS OF VIRAL SUBTYPE

Test	non-AG & AG-Plus		AG		Cohen's d (95% CI)	P Value	Adj. P Value
	N	Mean (SD)	N	Mean (SD)			
Attention/WM Domain							
PASAT Correct	63	45.8 (10.8)	86	48.1 (9.84)	0.23 (−0.10, 0.56)	0.173	0.173
Spatial Span Total	64	48.6 (11.6)	89	51.6 (9.93)	0.27 (−0.05, 0.60)	0.098	0.173
Attention Summary Score	63	47.1 (9.30)	86	50.0 (7.61)	0.35 (0.02, 0.68)	0.038	0.114
Learning Domain							
HVLT-R Total Recall	64	47.9 (11.2)	89	47.6 (10.1)	−0.02 (−0.35, 0.30)	0.884	0.884
BVMT-R Total Recall	64	46.7 (9.53)	89	49.0 (10.2)	0.23 (−0.09, 0.56)	0.158	0.316
Learning Summary Score	64	47.3 (8.72)	89	48.3 (8.01)	0.13 (−0.20, 0.45)	0.444	0.666
Memory Domain							
HVLT-R Delayed Recall	64	47.5 (11.3)	89	47.7 (9.72)	0.02 (−0.30, 0.34)	0.902	0.936
BVMT-R Delayed Recall	64	48.4 (11.2)	89	48.6 (10.9)	0.01 (−0.31, 0.34)	0.936	0.936
Memory Summary Score	64	47.9 (9.64)	89	48.1 (8.35)	0.02 (−0.30, 0.35)	0.893	0.893