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Association between brain volumes and HAND in cART naïve HIV+ individuals from Thailand

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Abstract

This study aimed to determine the effects of human immunodeficiency virus (HIV) on brain structure in HIV-infected individuals with and without HIV-associated neurocognitive disorders (HAND). Twenty-nine HIV-uninfected controls, 37 HIV+, treatment naïve, individuals with HAND (HIV+HAND+; 16 ANI, 12 MND, and 9 HAD) and 37 HIV+, treatment naïve, individuals with normal cognitive function (HIV+HAND−) underwent magnetic resonance imaging (MRI) and neuropsychological assessment. The HIV-infected participants had a mean (SD) age of 35(7) years, mean (IQR) CD4 count of 221(83-324) and mean (IQR) $\log_{10}$ plasma viral load of 4.81(4.39-5.48). Six regions of interest were selected for analyses including total and subcortical gray matter, total white matter, caudate, corpus callosum, and thalamus. The HIV+/HAND+ group exhibited significantly smaller brain volumes compared to the HIV-uninfected group in subcortical gray and total gray matter; however, there were no statistically significant differences in brain volumes between the HIV+HAND+ and HIV+HAND− groups or between HIV+/HAND− and controls. CD4 count at time of cART initiation was associated with total and subcortical gray matter volumes, but not with cognitive measures. Plasma viral load correlated with neuropsychological performance, but not brain volumes. The lack of significant differences in brain volumes between HIV+HAND+ and HIV+HAND− suggests that brain atrophy is not a sensitive measure of HAND in subjects without advanced immunosuppression. Alternatively, current HAND diagnostic criteria may not sufficiently distinguish patients based on MRI measures of brain volumes.

Keywords

HIV-associated neurocognitive disorder; neuroimaging; Thailand; cognition

Since the beginning of the HIV/AIDS epidemic, a substantial number of individuals have developed cognitive and neurological deficits, even in the absence of other AIDS-defining illnesses. The impact of HIV subtype B (HIV-B; primarily found in USA and Europe) on the brain has been well characterized in symptomatic and asymptomatic disease both pre-and post-treatment with combination antiretroviral therapy (cART; for review see Valcour, et al., 2011). However, other HIV subtypes are regionally distinct and have not had extensive characterization of cognitive or structural brain changes. In Thailand, greater than 90% of HIV cases are infected with a circulating recombinant form (CRF) 01_AE, often referred to as subtype E (Wirachsilp, 2007). The reported prevalence of cognitive impairment in Thailand has varied with an early study reporting 23% (Maj et al., 1994) and a more recent

study showing 6% (Vivithanaporn et al., 2010) In general, this prevalence is much lower than the 36-45% reported in other settings (Heaton et al, 2010). These differences may be due to the categorization of neurocognitive disorders or testing methodologies. An alternative explanation is that each subtype of HIV carries mutations in the coding of viral proteins, with certain mutations thought to affect the ability of the virus to enter and impact the CNS. One study of subtype E viral structure suggests this subtype might differentially impact the central nervous system (Ranjbar et al., 2006) due to the differences in TNF expression in HIV-E that would decrease risk for HIV-associated neurocognitive disorders (HAND). To date, there are no clinical studies indicating HIV-E would confer a differential risk for HAND compared to other HIV subtypes.

In 2007, the current guidelines for categorizing HAND were developed (Anitori et al., 2007) and three sub-groups were described: 1) Asymptomatic Neurocognitive Impairment (ANI), 2) Mild Neurocognitive Disorder (MND), and 3) HIV-associated Dementia (HAD). While attribution of confounding and contributing factors were noted, the nosology does not fully exclude such cases, and subsequent work has revealed that the probability of HAND increases substantially among subjects with confounding factors (Heaton et al., 2010). Thus, the HIV-specificity of these diagnostic criteria, in the absence of effective biomarkers, can be questioned. With these criteria, multiple domains of cognition should be assessed, in addition to functional impairment to appropriately categorize cases. In resource-limited settings, adequate normative data or relevant measures of functional status required to accurately assess HAND may not exist; thus, studies of HAND are lacking outside of developed countries. Similarly, limited information is known about the neuroimaging correlates of HAND outside of North America, especially in Southeast Asia.

Previous neuroimaging studies in Thailand have largely focused on magnetic resonance spectroscopy (MRS) with an early study demonstrating metabolite abnormalities between asymptomatic HIV+ (naïve to cART) and HIV-uninfected individuals, indicating neuronal loss and cellular injury (Sunwanwelaa, et al. 2000). More recent MRS studies reveal elevations in metabolites suggestive of cellular inflammation during acute HIV infection (Valcour et al., 2012; Sailasuta et al., 2012) that resolved after early cART (Sailasuta et al., 2012). A separate Thai neuroimaging study reported reduced regional brain volumes in cART naïve HIV+ individuals who had higher levels of peripheral HIV DNA compared to HIV+ individuals with lower HIV DNA levels (Kallianpur, 2014). However, prior studies did not characterize HIV+ by HAND status or compare brain volumes in HIV+ individuals, with and without HAND to HIV− uninfected individuals in Thailand.

This study aimed to examine HIV-related alteration in brain structure among HIV+ adults with HAND (HIV+/HAND+) and cognitively normal HIV+ adults (HIV+/HAND−) compared to HIV-uninfected (HIV−) controls in Thailand. Drawing from previous Thai neuroimaging studies utilizing magnetic resonance spectroscopy (Suwanwela et al. 2000; Valcour et al, 2012) and the extensive literature examining brain volume reductions in HIV-B (for review see Holt, Kraft-Terry, Chang 2012), we hypothesized that in this cohort infected predominantly with HIV-E , those with HAND would have reduced brain volumes in the following regions of interest (ROI): total gray matter, total subcortical gray matter, total white matter, caudate, putamen, and the thalamus.

Methods

HIV-infected participants were recruited by the Thai Red Cross AIDS Research Centre in Bangkok, Thailand. The HIV-uninfected participants were recruited through local advertising and from clients of the HIV testing clinic at the Thai Red Cross AIDS Research Center who were confirmed seronegative. Participants were enrolled into one of two studies (NCT00777426 and NCT00782808) after screening for HAND and intracellular HIV DNA levels, respectively and an enrollment scheme that included a range of HIV DNA. Specific methods for the recruitment of the study population have been previously reported (Valcour et al., 2013). HIV+ subjects were required to have CD4 count of <350 cells/mm^3 or symptomatic HIV, in accordance with Thai Ministry of Public Health criteria with the intent to initiate therapy within a month of enrollment. All participants had standard laboratory blood draws from which a complete blood count, CD4 cell count, plasma viral load (VL) were extracted. Forty-one participants elected to have lumbar puncture to obtain CSF viral loads were obtained. Both plasma and CSF HIV VL were quantified using the Amplicor HIV-1 Monitor Assay (Roche Molecular System, INC., Branchburg, NJ). Individuals were excluded (for both HIV+ and HIV uninfected groups) if they had a history of head injury (loss of consciousness >1 hour), positive urine illicit drug screen (checked during screening and enrollment), acute illness, significant laboratory abnormalities (e.g. creatinine, ALT, hemoglobin), a medical condition that could explain cognitive decline (e.g. hypothyroidism, B12 deficiency), pre-existing neurologic or psychiatric conditions, learning disability, positive hepatitis C screen, or contraindications for MRI (e.g. pregnancy, presence of metal). One individual with a low titer (1:1) syphilis serology and normal cerebrospinal fluid white blood cell count and protein was referred for uncomplicated syphilis treatment before enrollment. Data in this report were obtained from 29 HIV-uninfected controls and 74 HIV+ individuals. HIV+ participants were classified into two groups: those with HAND (HIV+/HAND+; N=37) and those that were cognitively normal (HIV+/HAND−; N=37). The HIV+/HAND+ group was comprised of 9 individuals characterized as HAD, 12 as MND, and 16 as ANI based on procedures defined in detail below. Each participant completed structural MRI and comprehensive cognitive testing within 30 days of their screening and bloodwork and prior to initiating cART. All participants provided informed consent. Both studies were approved by the ethics committees of Chulalongkorn University, the Walter Reed Army Institute of Research and the Human research protection office at University of California San Francisco.

Neuropsychological Testing

Participants completed the WHO/NIMH/UCLA international battery (Maj et al., 1993, Maj et al., 1994a,b) consisting of measures designed to assess the following skills: motor speed and fine motor control, verbal and visual memory, attention, and cognitive flexibility, as previously described (Valcour et al, 2007). This battery was developed specifically for administration in cross-cultural settings and validated in five regions, including Bangkok (Maj et al., 1994b). For the purpose of the present study, the battery was modified to ensure cultural relevance for the word list task and the visual memory task was replaced with the Brief Visual Memory Task – Revised (BVMT-R). A trained nurse at each location administered all measures with quality assurance completed every six months and with staff

turnover. We calculated z-scores for each measure using normative data from over 300 Thai controls as previously described (Heaps et al., 2012). Composite z-scores for domains were created by averaging the z-scores for motor and psychomotor tasks (Finger Tapping, Timed Gait, Grooved Pegboard, Trails A, Color Trails 1), cognitive flexibility and fluency measures (block matrix, Color Trails 2, Digit Symbol, first names, animal naming) and learning and memory measures (AVLT learning and recall, BVMT-R learning, and recall). We averaged the z-scores from all measures to create a global measure of cognition (NPZ-global).

Cognitive characterization

The study physician performed HIV-targeted neurological examinations as developed by the AIDS Clinical Trials Group (ACTG; Ellis et al. 2005) in the US.

Individual HAND diagnoses were determined by consensus conference attended by the Thai clinical staff, the principle investigator (VV), a US HIV neurologist (DC), and a US HIV-trained neuropsychologist (RP) applying the Frascati (2007) diagnostic criteria. Clinical discernment was required to classify abnormalities as mild or moderate and determine adequate evidence of abnormalities were beyond normal test variation, and not due solely to confounding conditions. Consideration was made for multiple tests within a domain such that the average domain z-score described above was not the determining factor in deciding impairment. Functional assessments included questions of instrumental activities of daily living (from Katz, 1983, and Lawton and Brody, 1969) work and social function, including reports from an informant when possible. We defined the groups as follows: cognitively normal (NL), testing performance within expectations for age and educational attainment; ANI, performance lower than expected given normal test variation in at least two domains, but no evidence or patient report of functional impairment; MND, testing performance moderately abnormal (typically 1 to 2 SD below the normative data) in two cognitive domains plus evidence of functional impairment; HAD, performance of severe impairment (typically worse than −2 SD) in two cognitive domains with clear evidence of functional impairment.

MRI

All MRI data were obtained at Chulalongkorn Hospital on a GE Signa 1.5T scanner with the latest software and hardware versions that included an isotropic 3D MRI acquisition (3D spoiled gradient echo, sagittal plane with full brain coverage, minimum echo time with full echo, TR=20ms, flip angle=50 with resolution $1\times1\times1.4$ mm^3). Images were processed using Freesurfer 5.0 (Fischl, et al., 2004). Freesurfer processing included extraction of non-brain tissue, normalization of voxel intensity as a result of MR bias, transformation of each brain to Talairach space, and segmentation of subcortical white matter and deep gray matter volumetric structures using voxel identity probabilities. Proper segmentation was reviewed and manually edited using built in freesurfer data quality modification tools (tmkedit) to ensure accurate classification of structures.

ROIs chosen for statistical analyses included: total gray matter, subcortical gray matter, total white matter, caudate, putamen, and thalamus. Volumes for each ROI were normalized to adjust for differences in head size (Free et al, 1995).

Statistical Analysis

Using ANOVA, primary analyses examined differences between participant groups (HIV-uninfected controls, HIV+HAND+ and HIV+HAND−) on age, gender, education levels and intracranial volume (ICV). Both HIV+ groups were compared on CD4 count, CSF viral load (CSFVL, n= 41), and plasma VL using independent t-tests. Since VL and CSFVL had skewed distributions, they were $\log_{10}$ transformed ($\log_{10}$VL and $\log_{10}$CSFVL, respectively). ANOVAs comparing ROI volumes between the HIV infected and uninfected groups were conducted to examine the impact of HIV on the six selected ROIs. Correlational analyses were conducted to determine the relationship between the ROIs, markers of disease burden, and neuropsychological testing performance.

Results

Education, Gender, ICV, CD4 counts, and plasma VL were similar across cognitive groups in the HIV-infected subjects (**Table 1**); however our MND group had a very high proportion of females compared to the other groups and as such we chose to include gender as a covariate in our analyses. As expected, there were significant group differences for global neuropsychological performance (Table 2) with ANI, MND, and HAD groups all performing worse than the HIV+HAND− group. However, the ANI and MND groups did not significantly differ by severity of neuropsychological deficits in the global or domain scores. The HAD group performed worse than all other groups in the learning and memory, and processing speed domains (see Table 2). We correlated CD4 cell count and Log_{10}VL with performance on global neuropsychological performance as well as domain-specific performance and identified a modest inverse relationship between plasma Log_{10}VL and performance on measures of cognitive flexibility/fluency (r=−0.28, p=0.01).

We then examined group differences in the six selected ROIs using ANCOVA (gender as covariate) identifying differences between the HIV+HAND+ group and the HIV-uninfected controls in three of the six ROIs: total gray matter ($F_{(2,99)}$ = 5.57, p<0.01, η^2=0.1), subcortical gray matter ($F_{(2,99)}$ =4.79, p=0.01, η^2=0.9), and a trend level difference in the thalamus ($F_{(2,99)}$ =2.96, p=0.056, η^2=0.06). There were no significant differences between the HIV+HAND+ and HIV+/HAND− groups. Additionally, there were no differences between the HIV+HAND− group and HIV-uninfected individuals for any of the volumetric measures (Figure 1).

A supplemental analysis was conducted to determine if categorizing both HIV+ groups by functional impairment would result in significant volumetric differences. In these analyses we analyzed the HIV+HAND+ group by specific HAND diagnosis with the HIV/HAND− and ANI groups combined (cognitively normal and asymptomatic as “asymptomatic”) and the MND and HAD groups (cognitively “symptomatic”). Using ANCOVA to compare only the 3 ROIs that were significantly different in the prior analysis, significant differences remained in the total gray matter between the HIV− uninfected and both the symptomatic

(p<0.01) and asymptomatic groups (p=0.01). Similarly, significant differences in subcortical grey matter between the HIV-uninfected and asymptomatic (*p*=0.03) HIV+ groups and in the thalamus between the HIV-uninfected group and the symptomatic HIV+ group (p=0.02) were observed. There were no significant volumetric differences between the HIV+ groups (symptomatic vs. asymptomatic; Figure2).

Correlational analyses revealed a small, but significant positive relationship between pre-cART CD4 count and total gray matter (*r*=0.32, *p*<0.01) and thalamic volumes (*r*=0.27, *p*=0.02) among HIV-infected subjects (Figure3).

Discussion

The results of this study evidence an impact of HIV on cortical gray matter, subcortical gray matter, and the thalamus of cART-naïve individuals with HAND in Thailand, where most would be expected to have subtype E virus. While there has been some suggestion that HIV subtype, particularly clade C, differentially affects HIV neuropathogenesis (see Rao et al., 2008) current studies of subtypes B and C fail to identify important clinical cognitive (deAlmedia et al. 2013; Paul et al. 2014) or brain volume differences (Ortega et al., 2013) by subtype. Our results further demonstrate that HIV-infected individuals in Thailand where subtype E is prevalent have similar alterations in brain volumes comparable to those shown to be affected in subtypes B and C prior to the initiation of cART (Ortega et al., 2013). Subcortical brain atrophy has been a primary finding in HIV subtype B studies both pre and post cART (for review see Paul et al., 2002 and Tucker et al, 2004). The caudate has been related to neuropsychological impairment in a number of studies typically in individuals who had progressed to later stages of AIDS. No differences in caudate volumes were observed between the HIV+ and findings are also similar to findings by members of our group in South Africa (Heaps et al, 2012; Ortega et al 2013). The HIV+HAND+ group had smaller gray matter, subcortical gray and thalamus volumes than the HIV-uninfected group; however they did not have smaller volumes than the HIV+HAND− group. In our supplemental analysis, we categorized the groups differently by comparing those with MND and HAD to HIV cognitively normal and ANI and HIV-uninfected controls noting that both symptomatic and asymptomatic HIV+ individuals have smaller total gray and thalamic brain volumes than HIV-uninfected individuals.

Combining the ANI group with the HIV+/HAND− group resulted in a significant difference between the groups although there remained no differences between the symptomatic and asymptomatic groups as in the main analysis. The classification of ANI is somewhat debated, with some reports suggesting it may artificially inflate the prevalence of HAND (Gisslen, 2011; Meyer, 2013; Torti, 2011) and others indicating that individuals presenting as ANI are at a greater risk to become symptomatic and later be recategorized as MND or HAD (Grant, 2014). There is also the possibility that the ANI group is not categorically unique from the MND group (Foley, 2011); however, they may lack the insight to report functional impairments (Chiao, 2013). The results of this study indicate there is a significant difference in cognitive performance between the HIV+/HAND+ groups and the HIV+/HAND− group, but we identify no difference between the symptomatic (MND + HAD) and asymptomatic (HIV-normal + ANI) groups in terms of neuropsychological testing and brain

volumes. This further support that the difference is primarily that of identifying symptoms and brings into question some reports suggesting MND or HAD is a progression from ANI. This finding concurs with a recent paper noting no differences between ANI and MND on objective measures of function (Chaio, Wendelken, Valcour et al., 2013).

CD4 values had a modest, but positive association with brain volumes. As all individuals in the study were treatment-naive, CD4 values in this study are likely very close approximations of CD4 nadir. Historically, CD4 has been reliably associated with both brain abnormalities (Jernigan et al., 2011, Thompson et al., 2005) and cognitive function pre-cART (Childs et al., 1999). Since the advent of cART, CD4 nadir has frequently been reported as a better indicator of cognitive dysfunction (Valcour, et al, 2006). Although we did not identify a significant relationship between CD4 and neuropsychological testing measures, the association identified between CD4 and brain volumes has implications for cART initiation. Recently, treatment guidelines in the US and other areas have shifted to recommend cART to all HIV+ individuals, without regard to CD4 status (Thompson, 2012). The World Health Organization (WHO) recently issued recommendations for earlier cART with CD4 less than 500 cells/μL (WHO 2013). Our results suggest that as CD4 cell count decreases brain volumes are negatively impacted. This impact on the brain may be mitigated with earlier treatment.

Plasma VL has also historically been a reliable marker of brain abnormalities and cognitive impairment prior to the cART era (Childs, et al., 1999). No relationship between plasma VL and brain volumes in this cohort were observed, however, we found a modest association between VL and cognitive flexibility/fluency, with higher VL correlated with poorer performance on those measures. With cART, VL usually decreases and thus it may be necessary to establish the reliability of other clinical markers of HAND. Recent work in this cohort also identified that HIV DNA reservoir levels in circulating CD14+ cells (enriched with monocytes) correlate with cognitive diagnosis and brain atrophy, specifically in the nucleus accumbens, brainstem, and total gray matter (Kallianpur, et al., 2014).

Despite a clear effect of HIV on gray matter and thalamic volumes, the lack of significant difference in volumes between the HIV+/HAND+ group and the HIV+/HAND− group suggests that volumetric changes are common in HIV+ patients and other factors influence whether individuals will suffer cognitive sequelae. Early life nutrition, education, age at infection, and cognitive reserve may be some of the factors that influence development of cognitive disorders in HIV. We were not able to examine the influence of most of these factors in this study, as we did not have information about age at infection, or early life nutrition. One measure of early life development and brain reserve that has been used in studies of Alzheimer's disease is size of the brain vault, or intercranial volume as a measure of pre-morbid brain reserve capacity (Faris et al., 2012; Perneczky et al., 2010; Tate et al., 2011). In our cohort, we used ICV as a regression factor in normalizing brain volumes, but we also examined potential group differences in ICV and found no group differences. This suggests that to the extent those are accurate markers of brain reserve capacity and early life development those factors were not significantly related to the cognitive changes noted in this cohort. Thus, volumetric analyses are not a sensitive diagnostic tool for determining or predicting the development of HAND.

Larger differences may have emerged with a larger sample size and longitudinal studies may better inform the course of HAND and its relationship to brain volume measures. HAND is difficult to characterize, as individuals rarely fit perfectly into diagnostic categories. Additionally, the ability to measure functional impairment in the laboratory often proves difficult. This study used multiple assessments of functional capacity and proxy informants when available to help overcome this challenge. It may have been beneficial to include performance-based measures of functional capacity to improve HAND classification (Blackstone et al., 2012) as these are thought to be less biased by mood or lack of insight. However, culturally relevant, performance based measures were not available at the time of this study. Additionally, global neuropsychological performance may not vary greatly between groups. Our results indicate changes take place in the brains of HIV infected individuals naïve to cART prior to evidence of functional impairment, which is consistent with the literature in subtype B. These volumetric changes occur in regions previously identified to have metabolite abnormalities and parallel volumetric changes seen in other HIV subtypes (B, C; Heaps et al. 2012; Ortega et al. 2013).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Valcour V, Sithinamsuwan P, Letendre S, Ances B. Pathogenesis of HIV in the central nervous system. Current HIV/AIDS Reports. 2011; 8(1):54–61. [PubMed: 21191673]

Wirachsilp P, Kantakamalakul W, Foongladda S, Chuenchitra T, Kohriangudom S, Athipanyasilp N, Sutthent R. Surveillance of subtype and genetic variation of the circulating strains of HIV-1 in Thailand. Southeast Asian J Trop Med Public Health. 2007; 38:814–827. [PubMed: 18041297]

Ranjbar S, Rajsbaum R, Goldfeld AE. Transactivator of transcription from HIV type 1 subtype E selectively inhibits TNF gene expression via interference with chromatin remodeling of the TNF locus. The Journal of Immunology. 2006; 176(7):4182–4190. [PubMed: 16547255]

Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, Grant I. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy CHARTER Study. Neurology. 2010; 75(23):2087–2096. [PubMed: 21135382]

Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007; 69(18):1789–1799. [PubMed: 17914061]

Suwanwelaa N, Phanuphak P, Phanthumchinda K, Suwanwela NC, Tantivatana J, Ruxrungtham K, Hanvanich M. Magnetic resonance spectroscopy of the brain in neurologically asymptomatic HIV-infected patients. Magnetic resonance imaging. 2000; 18(7):859–865. [PubMed: 11027880]

Sailasuta N, Ross W, Ananworanich J, Chalermchai T, DeGruttola V, Lerdlum S, RV254/SEARCH 010 protocol teams. Change in brain magnetic resonance spectroscopy after treatment during acute HIV infection. PloS one. 2012; 7(11):e49272. [PubMed: 23229129]

Valcour V, Chalermchai T, Sailasuta N, Marovich M, Lerdlum S, Suttichom D, Ananworanich J. Central nervous system viral invasion and inflammation during acute HIV infection. Journal of Infectious Diseases. 2012; 206(2):275–282. [PubMed: 22551810]

Kallianpur KJ, Valcour VG, Lerdlum S, Busovaca E, Agsalda M, Sithinamsuwan P, Ananworanich J. HIV DNA in CD14+ reservoirs is associated with regional brain atrophy in combination antiretroviral therapy naive patients. AIDS. 2014; 500:14–00085.

Holt JL, Kraft-Terry SD, Chang L. Neuroimaging studies of the aging HIV-1-infected brain. Journal of neurovirology. 2012; 18(4):291–302. [PubMed: 22653528]

Maj M, D'Elia L, Satz P, Janssen R, Zaudig M, Uchiyama C, Chervinsky A. Evaluation of two new neuropsychological tests designed to minimize cultural bias in the assessment of HIV-1 seropositive persons: a WHO study. Archives of Clinical Neuropsychology. 1993; 8(2):123–135. [PubMed: 14589670]

Valcour VG, Ananworanich J, Agsalda M, Sailasuta N, Chalermchai T, Schuetz A, SEARCH 011 Protocol Team. HIV DNA reservoir increases risk for cognitive disorders in cART-naive patients. PloS one. 2013; 8(7):e70164. [PubMed: 23936155]

Maj M, Janssen R, Starace F, Zaudig M, Satz P, Sughondhabirom B, Sartorius N. WHO neuropsychiatric AIDS study, cross-sectional phase I: study design and psychiatric findings. Archives of General Psychiatry. 1994; 51(1):39–49. [PubMed: 8279928]

Vivithanaporn P, Heo G, Gamble J, Krentz HB, Hoke A, Gill MJ, Power C. Neurologic disease burden in treated HIV/AIDS predicts survival A population-based study. Neurology. 2010; 75(13):1150–1158. [PubMed: 20739646]

Valcour VG, Sithinamsuwan P, Nidhinandana S, Thitivichianlert S, Ratto-Kim S, Apateerapong W, Shikuma CM. Neuropsychological abnormalities in patients with dementia in CRF 01_AE HIV-1 infection. Neurology. 2007; 68(7):525–527. [PubMed: 17296919]

Heaps J, Valcour V, Chalermchai T, Paul R, Rattanamanee S, Siangphoe U, Ananworanich J. Development of normative neuropsychological performance in Thailand for the assessment of HIV-associated neurocognitive disorders. Journal of clinical and experimental neuropsychology. 2013; 35(1):1–8. [PubMed: 23113809]

Ellis RJ, Evans SR, Clifford DB, Moo LR, McArthur JC, Collier AC, Robertson K. Clinical validation of the NeuroScreen. Journal of neurovirology. 2005; 11(6):503–511. [PubMed: 16338744]

Katz S. Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. Journal of the American Geriatrics Society. 1983

Lawton MP, Brody EM. Assessment of older people: Self-maintaining and instrumental activities of daily living. Gerontologist. 1969; 9:179–186. [PubMed: 5349366]

Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993; 43:2412–2414. [PubMed: 8232972]

Richardson-Vejlgaard R, Dawes S, Heaton RK, Bell MD. Validity of cognitive complaints in substance-abusing patients and non-clinical controls: The Patient's Assessment of Own Functioning Inventory (PAOFI). Psychiatry research. 2009; 169(1):70–74. [PubMed: 19619901]

Shy ME, Blake J, Krajewski KEA, Fuerst DR, Laura M, Hahn AF, Reilly M. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology. 2005; 64(7):1209–1214. [PubMed: 15824348]

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. Cereb Cortex. 2004b; 14:11–22. [PubMed: 14654453]

Free SL, Bergin PS, Fish DR, Cook MJ, Shorvon SD, Stevens JM. Methods for normalization of hippocampal volumes measured with MR. American Journal of Neuroradiology. 1995; 16(4):637–643. [PubMed: 7611015]

Rao VR, Sas AR, Eugenin EA, Siddappa NB, Bimonte-Nelson H, Berman JW, Prasad VR. HIV-1 clade-specific differences in the induction of neuropathogenesis. The Journal of Neuroscience. 2008; 28(40):10010–10016. [PubMed: 18829958]

de Almeida SM, Ribeiro CE, de Pereira AP, Badiee J, Cherner M, Smith D, Ellis RJ. Neurocognitive impairment in HIV-1 clade C-versus B-infected individuals in Southern Brazil. Journal of neurovirology. 2013; 19(6):550–556. [PubMed: 24277437]

Ortega M, Heaps JM, Joska J, Vaida F, Seedat S, Stein DJ, Ances BM. HIV clades B and C are associated with reduced brain volumetrics. Journal of neurovirology. 2013; 19(5):479–487. [PubMed: 24078556]

Gisslén M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? BMC infectious diseases. 2011; 11(1):356. [PubMed: 22204557]

Meyer AC, Boscardin WJ, Kwasa JK, Price RW. Is It Time to Rethink How Neuropsychological Tests Are Used to Diagnose Mild Forms of HIV-Associated Neurocognitive Disorders Impact of False-Positive Rates on Prevalence and Power. Neuroepidemiology. 2013; 41(3-4):208–216. [PubMed: 24157541]

Torti C, Focà E, Cesana BM, Lescure FX. Asymptomatic neurocognitive disorders in patients infected by HIV: fact or fiction? BMC medicine. 2011; 9(1):138. [PubMed: 22204606]

Grant I, Franklin DR, Deutsch R, Woods SP, Vaida F, Ellis RJ, Heaton RK. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology. 2014:10–1212.

Foley JM, Wright MJ, Gooding AL, Ettenhofer M, Kim M, Choi M, Hinkin CH. Operationalization of the updated diagnostic algorithm for classifying HIV-related cognitive impairment and dementia. International Psychogeriatrics. 2011; 23(05):835–843. [PubMed: 21092351]

Chiao S, Rosen HJ, Nicolas K, Wendelken LA, Alcantar O, Rankin KP, Valcour V. Deficits in self-awareness impact the diagnosis of asymptomatic neurocognitive impairment in HIV. AIDS research and human retroviruses. 2013; 29(6):949–956. [PubMed: 23432363]

Jernigan TL, Archibald SL, Fennema-Notestine C, Taylor MJ, Theilmann RJ, Julaton MD, Grant I. Clinical factors related to brain structure in HIV: the CHARTER study. Journal of neurovirology. 2011; 17(3):248–257. [PubMed: 21544705]

Thompson PM, Dutton RA, Hayashi KM, Toga AW, Lopez OL, Aizenstein HJ, Becker JT. Thinning of the cerebral cortex visualized in HIV/AIDS reflects CD4+ T lymphocyte decline. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102(43):15647–15652. [PubMed: 16227428]

Childs EA, Lyles RH, Selnes OA, Chen B, Miller EN, Cohen BA, McArthur JC. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology. 1999; 52(3):607–607. [PubMed: 10025796]

Farias ST, Mungas D, Reed B, Carmichael O, Beckett L, Harvey D, DeCarli C. Maximal brain size remains an important predictor of cognition in old age, independent of current brain pathology. Neurobiology of aging. 2012; 33(8):1758–1768. [PubMed: 21531482]

Perneczky R, Wagenpfeil S, Lunetta KL, Cupples LA, Green RC, Decarli C, Kurz A. Head circumference, atrophy, and cognition Implications for brain reserve in Alzheimer disease. Neurology. 2010; 75(2):137–142. [PubMed: 20625166]

Tate DF, Neeley ES, Norton MC, Tschanz JT, Miller MJ, Wolfson L, Bigler ED. Intracranial volume and dementia: some evidence in support of the cerebral reserve hypothesis. Brain research. 2011; 1385:151–162. [PubMed: 21172323]

Blackstone K, Moore DJ, Heaton RK, Franklin DR, Woods SP, Clifford DB, Grant I. Diagnosing symptomatic HIV-associated neurocognitive disorders: self-report versus performance-based assessment of everyday functioning. Journal of the International Neuropsychological Society. 2012; 18(01):79–88. [PubMed: 22114912]

Valcour V, Yee P, Williams AE, Shiramizu B, Watters M, Selnes O, Sacktor N. Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection-The Hawaii Aging with HIV Cohort. Journal of neurovirology. 2006; 12(5):387–391. [PubMed: 17065131]

Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, Volberding PA. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society–USA panel. Jama. 2012; 308(4):387–402. [PubMed: 22820792]

World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. World Health Organization; Geneva: 2013. <http://www.who.int/hiv/pub/guidelines/arv2013/en/>

Heaps JM, Joska J, Hoare J, Ortega M, Agrawal A, Seedat S, Paul R. Neuroimaging markers of human immunodeficiency virus infection in South Africa. Journal of neurovirology. 2012; 18(3):151–156. [PubMed: 22528474]

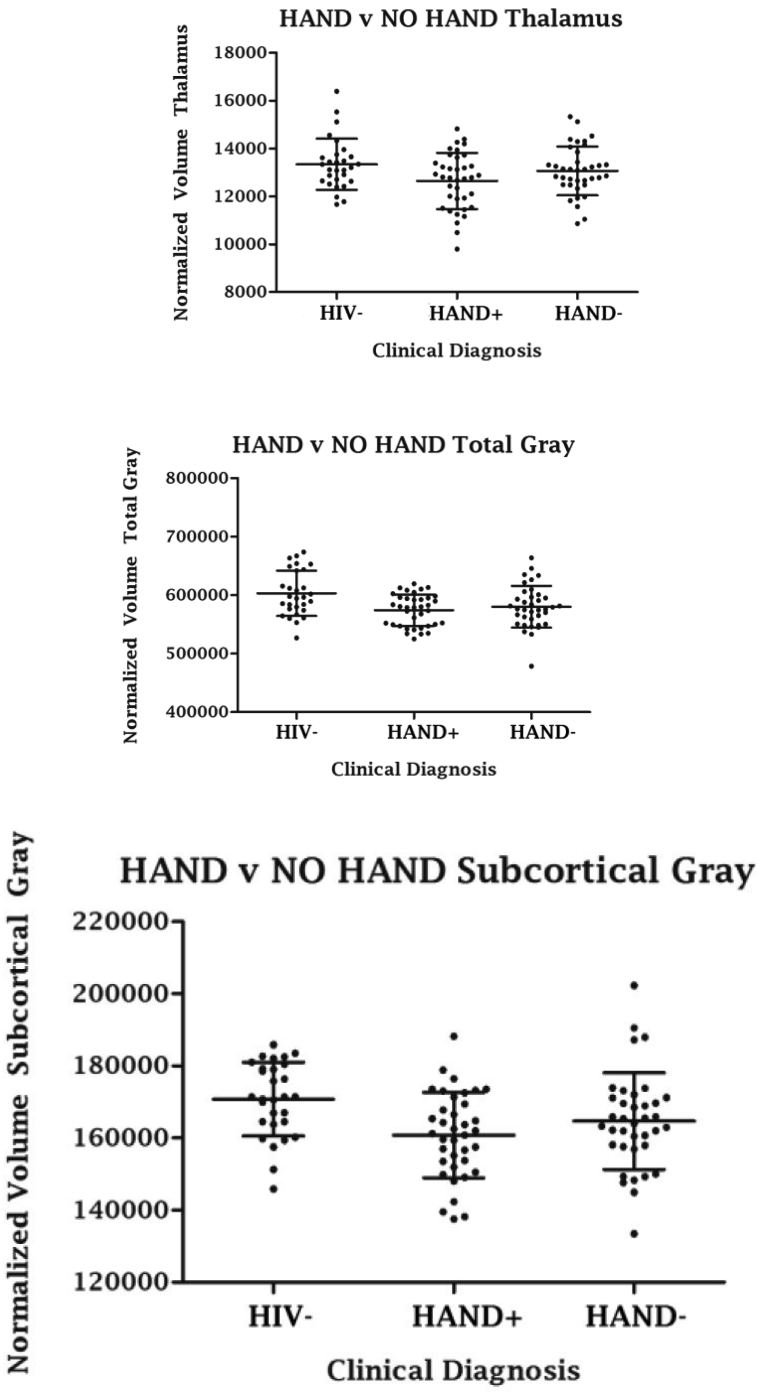

Figure 1.

shows scatter plots for the comparison of ROI volumes in the Thalamus, Total Gray matter, and Subcortical gray matter between the HIV−, HIV+HAND+, and HIV+HAND− groups. Significant differences existed between the HIV+HAND+ and HIV− groups only. Lines represent the group means (center) and standard deviations

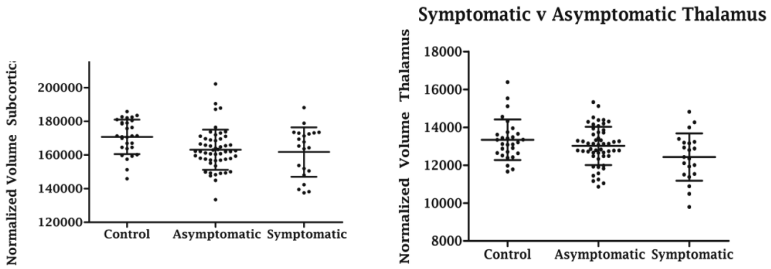

Figure 2.

shows scatter plots for the comparison ROI volumes between the HIV−, HIV+symptomatic HIV+S; MND and HAD), and HIV+asymptomatic (HIV+A; Normal cognition and ANI) groups. Significant differences were present in the thalamus and subcortical gray ROis between the HIV− and HIV+S groups as well as the HIV− and HIV+A groups. There were no significant differences between the HIV+ groups.

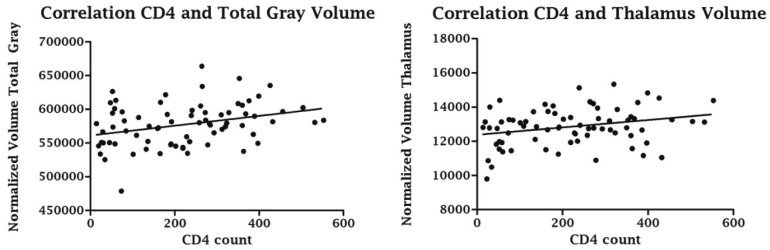

Figure 3.

shows the correlations between CD4 count and ROI volumes in the total gray matter and the thalamus for all HIV+ individuals.

Table 1

shows the demographic characteristics of the HIV+ (by HAND status) and the HIV− groups.

Age		HIV−	HIV+/HAND−	HIV+/HAND+	Sig.
	N	29	37	37	
	Mean (SD)	34 (6.4)	35 (6.3)	35 (8.1)	0.9
	Range	21-46	22-49	23-57	
Gender					
	% Female	44.8	51.4	62.2	0.36
Education					
	Mean	13 (4.1)	11 (4.6)	12 (3.7)	0.14
	Range	4-20 yrs	4-19 yrs	0-20 yrs	
CD4					
	Mean		232	210	
	IQR	.	204	287	0.5
	Range	.	19-553	14-532	
LogVL					
	Mean		4.66	4.96	
	IQR	.	1.08	0.83	0.07
	Range	.	3.15-5.88	3.15-5.88	
CSFVL					
	N	0	21	20	
	Mean		3.95	4.16	0.45
	IQR	.	1.49	1.12	
	Range	.	1.70-5.42	3.20-5.09	

**Significant mean differences between groups p<0.05

Table 2

shows Performance on neuropsychological measures by domain in the HIV+ groups by HAND status. Mean scores represent average z-scores of all measures included within the domain. All z-scores are based on normative data from age and education adjusted controls (Heaps et al. 2012)

		HIV Normal 37	ANI 16	MND 12	HAD 9
Fluency	Mean	0.37	−0.16	−0.44	−0.99
	SD	0.76	0.62	0.61	1.55
				*	**
Motor	Mean	0.07	−0.68	−0.65	−1.19
	SD	0.63	0.61	0.41	1.12
			*	**	
Executive Function	Mean	0.53	−0.83	−1.25	−2.99
	SD	1.05	0.84	0.81	1.39
				**	** *a*
Processing Speed	Mean	0.09	−0.39	−0.75	−2.25
	SD	0.64	0.53	0.77	0.81
				**	***a,b*
Learning & Memory	Mean	0.45	−0.19	−0.39	−1.59
	SD	0.66	0.65	0.81	0.73
			*	**	***a,b*

* p<0.05 compared to HIV+ normal

** p<0.01 compared to HIV+ normal

a p<0.01 compared to ANI

b p<0.01 compared to MND