Published in final edited form as:

J Neurovirol. 2013 October ; 19(5): . doi:10.1007/s13365-013-0202-x.

HIV Clades B and C are Associated With Reduced Brain Volumetrics

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Abstract

Objective—HIV has multiple genetic clades with varying prevalence throughout the world. Both HIV-clade C (HIV-C) and HIV-clade B (HIV-B) can cause cognitive impairment but it is unclear if these clades are characterized by similar patterns of brain dysfunction. We examined brain volumetrics and neuropsychological performance among highly active anti-retroviral therapy (HAART) naïve HIV-B and HIV-C participants.

Design—Thirty-four HAART-naïve HIV-infected (HIV+) participants [(17 HIV-B (United States); 17 HIV-C (South Africa)] and 34 age and education-matched HIV-uninfected (HIV–) participants were evaluated.

Methods—All participants underwent similar laboratory, neuropsychological, and neuroimaging studies. Brain volume measures were assessed within the caudate, putamen, amygdala, thalamus, hippocampus, corpus callosum and cortical (grey and white matter) structures. A linear model that included HIV status, region, and their interaction assessed the effects of the virus on brain volumetrics.

Results—HIV– and HIV+ individuals were similar in age. On laboratory examination, HIV-C participants had lower CD4 cell counts and higher plasma HIV viral loads than HIV-B individuals. In general, HIV+ participants performed significantly worse on neuropsychological measures of processing speed and memory and had significantly smaller relative volumetrics within the thalamus, hippocampus, and corpus callosum and cortical grey and white matter compared to respective HIV– controls. Both HIV-clades B and C are associated with similar volumetric declines when compared to matched HIV– controls.

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Conflicts of Interest: None to Declare

Author Contributions: M. Ortega designed, proposed and analyzed the project, wrote and revised the manuscript. J. Heaps analyzed the data and revised the manuscript. F. Vaida performed statistical analyses and revised the manuscript. R. Paul & J. Joska proposed the project and revised the manuscript; Seedat & D. Stein analyzed the data and revised the manuscript; B. Ances proposed and designed the project, supervised the project, wrote and revised the manuscript. S

Conclusions—HIV-B and C were associated with significant reductions in brain volumetrics and poorer neuropsychological performance; however, no specific effect of HIV clade subtype was evident. These findings suggest that HIV-B and HIV-C both detrimentally affect brain integrity.

Keywords

HIV clade; brain volumetrics; magnetic resonance imaging; neuropsychological performance

Introduction

The human immunodeficiency virus (HIV) crosses through the blood-brain barrier soon after infection, resulting in reactive neuroinflammation and subsequent neuronal death (Kaul et al. 2001; Kumar et al. 2009). Once in the brain, HIV primarily infects microglia and astrocytes rather than neurons (Kaul et al. 2001; Gougeon and Piacentini 2009; Anthony and Bell 2008). A subsequent cascade of inflammatory chemokines and cytokines induces excitotoxicity and neuronal loss (Kaul, Garden, and Lipton 2001; Mattson, Haughey, and Nath 2005). While the presence of the virus is ubiquitous throughout the brain, higher concentrations have been observed in the striatum and cortical grey and white matter (Wiley et al. 1998; Archibald et al. 2004) that comprise a frontal-subcortical network. Disruption of neuronal function in these networks can result in impairments in psychomotor performance, learning, and executive function (Arendt et al. 1990; Carey et al. 2004; Thompson et al. 2005; Becker et al. 2011; Cardenas et al. 2009; Ances et al. 2010; Ances et al. 2009; Stout et al. 1998; Avison et al. 2004; Cohen et al. 2010; Gongvatana et al. 2011).

Several HIV clade subtypes have evolved with distinct genetic differences that follow geographic boundaries (Shapshak et al. 2011; Rambaut et al. 2004; Wainberg 2004). HIV clade C (HIV-C) is the most prevalent clade worldwide and exists primarily in India, Southern Africa, and portions of North America (Wainberg 2004). HIV clade B (HIV-B) is predominantly found in the United States (US) and Europe. A majority of HIV research concerning neurocognitive disorders has primarily focused on HIV-B. These two HIV subtypes have distinct viral structures that may account for differences in their neurovirulence (Campbell et al. 2011; Mishra et al. 2008; Rao et al. 2008). In animal studies, HIV-C is less virulent than HIV-B due to reductions in monocyte attraction (Rao et al. 2008), induction of fewer pro-inflammatory cytokines (Gandhi et al. 2009), and decreased replication within monocytes (Constantino et al. 2011). Additionally, animals infected with HIV-C have better cognitive performance than HIV-B infected animals (Rao et al. 2008).

Within humans, HIV-associated neurocognitive disorders (HAND) have been observed with both clade subtypes. However, controversy remains as the prevalence of HAND varies within these subtypes with an occurrence of 33-50% for HIV-C (Joska et al. 2011) and 22-55% for HIV-B (Heaton et al. 2010; Antinori et al. 2007). Observed distinctions in cognitive impairment may reflect differences in sample heterogeneity or study designs that did not include comparable controls with similar cultural and educational backgrounds (Heaton et al. 2010). Furthermore, educational and cultural differences can complicate neuropsychological assessments as most tests that have been developed are based on controls from the US population. As such, non-behavioral biomarkers could also assist in identifying HIV-associated neuropathology according to HIV clade subtype independent of neuropsychological assessment.

Neuroimaging provides a non-invasive method to assess the effects of HIV in the brain. In general, brain integrity is affected by HIV even in the highly active anti-retroviral therapy

(HAART) era (Ances et al. 2012; Thompson et al. 2005; Becker et al. 2011; Cardenas et al. 2009; Chang et al. 2011; Stout et al. 1998; Pfefferbaum et al. 2009). However, most neuroimaging studies have been performed in the US or Europe where HIV-B is most prominent. Structural changes due to HIV-B have been seen within select cortical and subcortical areas (Thompson et al. 2005; Stout et al. 1998; Archibald et al. 2004; Cardenas et al. 2009; Ances et al. 2012). More recently, our group has demonstrated significant decreases in both cortical (grey and white matter) and subcortical (i.e. thalamus) areas in HIV-C individuals when compared to appropriate HIV- controls (Heaps et al. 2012). Furthermore, members of our group have reported microstructural abnormalities in the white matter of HIV-C participants (Hoare et al. 2012). However, studies comparing HIV-B and HIV-C have not been completed.

In this current study we examined volumetric measures, laboratory values, and neuropsychological performance within HAART naïve HIV-B and HIV-C individuals. In order to compare structural changes that occur in each cohort, HIV- controls from both regions (US and South Africa) were included. We hypothesized that both HIV+ individuals (HIV-B and HIV-C) would have poorer cognitive performance and reductions in brain volumetrics relative to HIV- controls.

Methods

Participants

A total of 68 participants were included in this study. Participants were recruited from both the US (n=34) and South Africa (n=34). Within each country, 17 HAART-naïve HIV+ individuals and 17 HIV- controls matched for age and education were included. Gender differences existed between the HIV-B and HIV-C groups. The HIV-B group was entirely male and a majority of the HIV-C participants were female (65%). HIV- controls were matched regionally for gender, such that a majority of HIV- controls in the US were male (76%), and a majority of the HIV- controls in South Africa were female (65%).

Participants with a history of head injury with loss of consciousness > 30 minutes, major psychiatric disorders, opportunistic central nervous system infections, or contraindications for MRI scanning (metal implants in head, pacemakers, claustrophobia, etc.) were excluded. Consent was obtained from all participants using forms approved by the appropriate Human Research Ethics Committee in Cape Town, South Africa, and the institutional review board (IRB) for the participating US based universities. For all HIV+ participants, HIV status was confirmed through enzyme-linked immunoassay (ELISA), western blot, or polymerase chain reaction.

Clinical measurements

Laboratory evaluations of plasma CD4 cell count and plasma HIV viral load (VL) were obtained within 3 months or less of neuroimaging for all HIV+ individuals. Neuropsychological performance testing was completed within 1 week or less of neuroimaging. Duration of infection (time since infection to MRI scan) was based on participant recall. Blood was drawn from each of the participants to determine CD4 cell count and HIV viral load (VL).

Neuropsychological performance testing

All participants were administered similar neuropsychological tests to assesses the following cognitive domains: Learning [(Hopkins Verbal Learning Test-Revised (HVLTR))], Psychomotor speed (Digit Symbol and Trails A), and Verbal fluency (Animal Fluency; Table 1)(Ances et al. 2012; Heaps et al. 2012). In South Africa, the HVLTR was adjusted

to ensure items were culturally relevant by using semantically related words occurring with similar frequency in the Xhosa language compared to words used in the English version. Additionally, word choices and instructions for tests were first translated from English to Xhosa (the primary language spoken by our patient sample in South Africa) with reverse translation, Xhosa to English, and translated back to English to verify accuracy (Heaps et al 2012, Joska et al 2011).

Structural neuroimaging

In the US, imaging was performed on a 3T Siemens Tim Trio whole body MR scanner (Siemens AG, Erlangen Germany) with a 12 channel transmit/receive head coil. The structural images were acquired using a T1-weighted 3-dimensional magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence [time of repetition (TR) = 2400ms, echo time (TE) = 3.16ms, inversion time (TI) = 1000ms, flip angle = 8 degrees, 162 slices, and voxel size = $1 \times 1 \times 1\text{mm}^3$]. All images were acquired in the sagittal plane. In South Africa, imaging was acquired on a 3T Siemens Allegra MR scanner (Siemens AG, Erlangen Germany), with a 4 channel head phased head coil using an identical MP-RAGE sequence as noted above, except for TE = 2.38ms. These scans were also acquired in the sagittal plane. During these scans participants were instructed to focus on a plus (+) sign in the center of the screen in order to reduce movement. If excessive movement was observed an additional structural scan was acquired.

Quantification of volumes within certain regions was completed using the Freesurfer software suite (v5.1) (Martinos Center, Harvard University, Boston, MA; <http://surfer.nmr.mgh.harvard.edu>). Briefly, this well validated automated software program transforms the MP-RAGE scan of an individual into a template space with the skull stripped and the brain segmented into white matter, grey matter, and ventricles. Brain regions were parcellated into subcortical and cortical regions of interest (ROI) using a surface deformation program (Fischl et al. 2002; Desikan et al. 2006; Fischl and Dale 2000). Images from all subjects were aligned onto a common atlas (MNI305) (Fischl et al. 2004). For this analysis, strategic ROIs analyzed included: caudate, putamen, amygdala, thalamus, hippocampus, corpus callosum, grey matter, and cortical white matter. Two trained raters independently confirmed the segmentation of these ROIs (MO and JMH) with manual edits implemented when necessary. Each volume was normalized to total intracranial volume using a least square residual regression model (Ances et al. 2012).

Statistical Analysis

For each ROI, the effect of HIV infection on brain volumetrics was assessed using a linear model, with the log-transformed ROI volume used as the response. The natural logarithm transformation achieves two important goals. First, it improved normality and homoscedasticity of the volumetric outcome. Second, it allowed the interpretation of the results in terms of proportional differences between groups. Specifically, if β was the regression coefficient for the HIV indicator in the analysis of the natural log-transformed volume, then $\exp(\beta)$ was the ratio of the mean volumes of the HIV+ and HIV- groups, and $\exp(\beta)-1$ was the proportional or fractional difference in mean volumes between groups. The mean here refers to the geometric mean. For HIV and other factors we reported the effect $\exp(\beta)-1$. For example, a negative effect of HIV represented volume “reduction” due to HIV and a positive effect represented volume “increase”. This methodology allowed us to compare the effects of HIV clades between the two groups, even though the volumetrics of the two groups were not directly comparable. 95% confidence intervals were also included.

The linear model included HIV status (ie HIV+ or HIV-), region (US versus South Africa), and their interaction. The region effect allowed for overall volumetric differences between

the US and South Africa in the HIV– controls. The interaction between HIV status and region compared the effects of the HIV-B and HIV-C clades on brain volumes in their respective populations. The statistical presence of an interaction signified that the HIV-B and HIV-C clades had different effects on brain volumes. If this interaction was not significant ($p < 0.05$ level), it was removed from the model, and an additive model that included HIV status and region as covariates assessed the effects of HIV, adjusting for volume differences between the South Africa and US regions among the HIV– controls. Based on these models we reported: (i) the clade effect (given by the interaction between HIV status and region); (ii) the HIV effect (differences between HIV+ and HIV– controls, when these did not differ between clades). Our analyses adjusted for gender, age, and years of education using backward model selection with a significance threshold of 0.20.

The effect of CD4 cell count on brain volumetrics within HIV+ participants was examined separately for each region using a linear model with square root-transformed CD4 cell counts as a predictor and the ROI log-transformed volume as a response. The square-root transformation is typically used in the analysis of CD4 data in order to improve normality of the distribution. (Ellis et al. 2011) We also examined for possible differences between regions in regards to the association between CD4 cell count and brain volumetrics using a similar linear model that included square root CD4 cell count, region (US versus South Africa), and their interaction. Similar analyses were conducted for the association between $\log_{10}$ plasma HIV viral load and brain volumetrics. Finally, we studied the association between duration of infection (log-transformed) and brain volumetrics for both regions using similar methods as mentioned above for the CD4 cell count effect. For the duration of infection we used a base 2 logarithm transformation, such that a single unit on the $\log_2$ scale represented a doubling of time since infection.

Results

HIV-C individuals had greater compromised immune system

Demographics for the various groups are presented in Table 1. In general, the groups were similar with regard to age and education. HIV-C individuals had significantly lower plasma CD4 cell counts and significantly higher plasma HIV VL than HIV-B participants. The self-reported time since diagnosis (estimated duration of HIV infection) was not significantly different between the two HIV+ groups, with the mean, minimum, and maximum of 14 months (2,14) and 17 months (5,23) for HIV-C and HIV-B respectively. (Table 1).

Neuropsychological performance was lower in HIV+ individuals

Significant differences on neuropsychological measurements were observed between HIV+ individuals (regardless of HIV clade subtype) and HIV– controls. In particular, both HIV-B and HIV-C individuals performed significantly worse than their HIV– control counterparts on Digit-Symbol, Animal Fluency, and Trail Making A (Table 1). Due to the differences in education as well as potential cultural differences that may exist between the two regions, neuropsychological measures could not be directly compared between the US and South Africa cohorts.

Brain volumetrics were lower in HAART-naïve HIV+ individuals compared to HIV– controls

HIV+ individuals (regardless of HIV clade subtype) had significantly smaller measurements in brain volumetrics within multiple ROIs compared to HIV– controls (Table 2). The thalamus, corpus callosum, hippocampus, gray matter and cortical white matter were significantly reduced in HIV-C individuals compared to respective South African HIV– controls (Supplementary Figure 1). HIV-B individuals had a significantly smaller proportional volume only within the gray matter when compared to the HIV– controls in the

US (Table 2 and Supplementary Figure 1). However, no significant differences in brain volumes were observed between HAART-naïve HIV-B and HIV-C individuals after adjusting for demographics. Overall these findings are reported in the mean and interquartile differences (volumetric) between respective HIV+ and HIV- groups (Supplementary Figure 1.), as well as the percent difference between groups (see Table 2.).

Laboratory indices did not correlate with brain volumetric measures in HIV+ individuals

No significant associations were observed for plasma CD4 cell count or plasma HIV VL and brain volumetrics for each of the ROIs regardless of the HIV clade subtype (data not shown). As expected, with the matched durations of infection between the two HIV clades (Table 1), there was no observed association between duration of HIV infection and brain volumetrics for each of the ROIs (data not shown).

Discussion

In the present study we observed significantly smaller volumes in both subcortical (HIV-C) and cortical areas (HIV-B and HIV-C) for HIV+ individuals compared to HIV- controls. No significant differences in brain volumes were seen between HIV-B and HIV-C participants. Our study suggests that HIV-B and HIV-C are both neurovirulent and are associated with reductions in brain volumetrics and neuropsychological performance.

Previous studies have suggested that both HIV-B and HIV-C diminish cognitive performance; however, animal models have suggested that HIV-C is less neurovirulent than HIV-B (Rao et al. 2008; Mishra et al. 2008). Multiple human studies performed in the US have demonstrated HAND is prevalent for HIV-B and HIV-C. Neuropsychological deficits have also been observed in HIV-C human studies performed in India (Wadia et al. 2001; Yepthomi et al. 2006) and Africa (Joska et al. 2011;). However, in Africa, the prevalence of HAND is difficult to accurately assess due to the lack of established normative data that are region-specific. In this study HIV+ individuals were more impaired, regardless of clade subtype, across multiple cognitive domains compared to HIV- controls (Table 1). Interestingly, similar cognitive domains were affected in HIV-B and HIV-C individuals when compared to their respective HIV- control group despite using a relatively restricted battery. Although the neuropsychological tests were administered in a standardized manner, we chose not to directly compare performance between the two HIV clades considering the cultural and educational differences that exist between the countries as well as the lack of established normative neuropsychological data in South Africa.

Neuroimaging provides an objective method for assessing brain abnormalities and the magnitude of these abnormalities between HIV clades. Previous studies have demonstrated reduced volumes within the thalamus, caudate, putamen, cortical white matter, and gray matter due to HIV-B (Thompson et al. 2005; Clark et al. 2012; Towgood et al. 2012; Pfefferbaum et al. 2012; Stout et al. 1998; Ances et al. 2012; Holt et al. 2012) (for review see Holt et al. 2012). However, only a few studies have investigated the effects of other clades besides HIV-B using neuroimaging (Heaps et al. 2012; Hoare et al. 2012). Our group has recently shown that HIV-C individuals have smaller brain volumetric measures within the thalamus, white matter, and gray matter (Heaps et al. 2012). The current study is a natural extension of this work as it is the first to investigate if the relative differences in brain volumes are different for HIV-B and HIV-C. We observed significant reductions in subcortical and cortical areas that were similar to previous reports in the US and South Africa; however no significant differences were seen between clade subtypes across ROIs (Table 2 and Supplementary Figure 1). While the relative differences in HIV-C were larger for all ROIs except the amygdala, none of the differences were significant across the clades. These findings suggest that HIV negatively impacts brain integrity for both clades despite

genetic differences. These neuroimaging results appear to contradict recent literature showing that HIV-B and HIV-C impart different levels of toxicity at the cellular level (Samikkannu et al. 2011; Rao et al. 2008, Rao et al. 2013). Differences in neurovirulence may still occur as our study only focused on HIV+ individuals that had been infected for a relatively short period of time and were HAART naïve. Further, while previous studies of HIV-C toxicity focused on a defect in the Tat protein that appears to underlie reduced neuronal damage. It is possible that geographic differences exist in the conservation of this Tat protein defect. The frequency of the HIV-C Tat protein defect may be less common among individuals in South Africa than what has been previously reported among HIV+ individuals in India (Gandhi et al. 2009; Rao et al. 2013). Nevertheless, the fact that cognitive impairments have been reported across multiple geographic regions suggests that factors other than Tat underlie compromised brain integrity associated with HIV-C (Mishra et al. 2008; Jayadev and Garden 2009; Modi et al. 2007)

In the present study both HIV+ participants had poorer immune function as assessed by current CD4 cell count and HIV VL. For this study we only focused on HIV+ participants who were HAART naïve in an attempt to reduce possible confounding effects of medications. Recently studies have suggested early initiation of HAART could reduce the incidence of HAND (Heaton et al. 2010; Crum-Cianflone et al. 2012). Interestingly, there was no significant relationship between plasma HIV VL or current plasma CD4 cell count, and brain volume for either HIV-B or HIV-C. These peripheral measures may not be sensitive to changes that occur within the brain. It is also possible that our small sample size may have limited ability to detect the relationship between these markers and brain abnormalities. Additionally, we did not observe a significant relationship between duration of infection and brain volumes for select ROIs. Duration of infection was estimated from self-reported time since diagnosis for the majority of HIV+ participants and may be subject to recall bias.

Our study has a few limitations. In general, a relatively small number of participants (n=17) were present within each of the groups. Years of education were significantly different between the two countries though differences in educational school systems limit direct comparisons of education such that the group difference is not as meaningful in the case of intra-clade comparisons. A significant strength is that these groups are relatively well balanced with regard to age. An additional strength was that all neuroimaging studies were acquired on the same scanner manufacturer, at the same field strength, and with similar imaging acquisition. In the US, a greater proportion of HIV+ participants were male, whereas in South Africa more were female. While we were able to control for age and gender within each continent, additional socioeconomic differences could exist between the two continents. In particular, differences in diet, health care access, and culture are disparate between the two groups. In this sample we could not obtain nadir CD4 cell count for the HIV-C group due to limited access to medical care, as participants were referred from various clinics. A well matched HIV- control group from respective areas was included to mitigate some of these differences. For our analysis, we compared brain volumes to age and sex matched local controls within each clade and then compared the relative difference in brain volume between the HIV+ groups to account for possible regional differences. Finally, our analysis was restricted to primarily cortical and subcortical volumetrics and not cortical thickness. Future studies using cortical thickness may be beneficial for determining if clade differences exist (Thompson et al. 2005; Kallianpur et al. 2012; Ances et al. 2009; Wang et al. 2011). Since the current study is cross-sectional in nature, we are unable to determine if a particular HIV clade subtype augments the amount of degeneration.

In summary, this study demonstrates there are similar degrees of brain abnormalities in both HIV-B and HIV-C who were HAART naïve. These changes exist independent of typical

peripheral markers such as plasma HIV VL or plasma CD4 cell count. Based on the small neuropsychological battery administered it is evident that both HIV-B and HIV-C groups demonstrate deficits compared to their respective HIV– controls. Further longitudinal studies are needed to assess the impact of HAART on both brain imaging metrics and neuropsychological performance in these cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: Supported by the National Institute of Mental Health (K23MH081786 to B.M.A., R01MH22005 to F.V., R01MH085604 to R.P.); National Institute of Nursing Research (R01NR012907, R01NR012657, and R01NR014449 to B.M.A.); National Institute of Allergy and Infectious Disease (R01AI47033 to F.V.); National Institute of Health (MH065857 to R.P., J.J., and J.M.H.); Grossman Chancellor's Fellowship (M.O.); National Science Foundation IGERT (0548890 to M.O.)

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Figure 1.

Regions of interest that were evaluated for each participant included the corpus callosum (red), caudate (light blue), thalamus (green), putamen (pink), hippocampus (yellow), and amygdala (aqua). Areas of interest were overlaid onto a sagittal T1 magnetization-prepared rapid acquisition gradient echo magnetization-prepared rapid acquisition gradient echo (MPRAGE) image.

Table 1

Demographics of participants

Clade C (South Africa cohort)			Clade B (US cohort)	
	HIV- (n=17)	HIV+ (n=17)	HIV- (n=17)	HIV+ (n=17)
<i>Demographics</i>				
Age Mean, SD	25 ± 6	28 ± 3	29 ± 7	29 ± 7
% Male	35	35	76	100
Education (years), SD	11 ± 1	10 ± 2	14 ± 3	13 ± 2
<i>Clinical Measurements</i>				
Log ₁₀ Plasma HIV Viral Load mean, quartiles	-	4.50 (4.19, 5.06)	-	3.89 (3.52, 4.21) ^a
Plasma CD4 cell count cells/mL (quartiles)	-	186.6 (95, 253)	-	349.2 (278, 388) ^b
Self-reported Duration of Infection months (minimum, maximum)	-	14 (2, 14)	-	17 (5, 23)
<i>Raw Neuropsychological Performance</i>				
Hopkins Verbal Learning Task Revised # correct (SD)	22.1 (2.9)	22.1 (5)	24.9(7.3)	23.9(5.1)
Digit Symbol # correct (SD)	47.3 (11.1)	22.7 (8.9) ^c	79.9 (16.6)	68.1 (16.8)
Trails A seconds (SD)	39.6 (12.3)	53.0 (16.8) ^d	22.3 (7.1)	34.0 (13.3) ^e
Animal Fluency # correct (SD)	18.1 (5.1)	13.9 (3.7) ^d	24.8 (5.5)	19.5 (6.9) ^f

SD= standard deviation

^a *p*-value <0.05 for HIV-B+ and HIV-C+^b *p*-value <0.01 across HIV-B+ and HIV-C+^c *p*-value <0.001 between HIV-C and HIV- control group in South Africa^d *p*-value <0.01 between HIV-C and HIV- control group in South Africa^e *p*-value <0.005 between HIV-B and HIV- control group in US^f *p*-value <0.05 between HIV-B and HIV- control group in US

Table 2

The effect of HIV clade subtype on brain volumes

ROI Volumetrics	HIV-B vs HIV- controls	HIV-C vs. HIV- controls	HIV-B vs. HIV-C	HIV+ vs. HIV- overall
GRAY MATTER Relative Difference, [95%CI] p-value	-0.042 [-0.076, -0.007] p=0.022	-0.085 [-0.116, -0.052] p<0.001	0.047 [-0.004, 0.1] <i>p=0.072</i>	-0.064 [-0.087, -0.04] p<0.001
CORPUS CALLOSUM Relative Difference, [95%CI] p-value	-0.051 [-0.145, 0.054] p=0.316	-0.108 [-0.186, -0.022], p=0.016	0.064 [-0.071, 0.219] p=.	-0.08 [-0.14, -0.015] p=0.017
CAUDATE Relative Difference, [95%CI] p-value	-0.049 [-0.121, 0.029] p=0.2	-0.033 [-0.099, 0.037] p=0.33	-0.016 [-0.113, 0.091] p=0.75	-0.041 [-0.089, 0.009] p=0.11
AMYGDALA Relative Difference, [95%CI] p-value	-0.061 [-0.147, 0.033] p=0.186	-0.016 [-0.063, 0.033] p=0.502	-0.046 [-0.141, 0.06] p=0.375	-0.039 [-0.088, 0.013] p=0.135
WHITE MATTER Relative Difference, [95%CI] p-value	-0.034 [-0.08, 0.014] p=0.156	-0.073 [-0.121, -0.023] p=0.006	0.042 [-0.029, 0.118] p=0.246	-0.054 [-0.087, -0.02] p=0.003
THALAMUS Relative Difference, [95%CI] p-value	-0.024 [-0.089, 0.047] p=0.488	-0.107 [-0.16, -0.051] p=0.001	0.093 [-0.002, 0.197] <i>p=0.054</i>	-0.066 [-0.108, -0.022] p=0.004
HIPPOCAMPUS Relative Difference, [95%CI] p-value	-0.086 [-0.221, 0.072] p=0.259	-0.111 [-0.179, -0.037] p=0.005	0.028 [-0.137, -0.225] p=0.754	-0.099 [-0.174, -0.017] p=0.02
PUTAMEN Relative Difference, [95%CI] p-value	-0.001 [-0.084, 0.09] p=0.99	-0.026 [-0.085, 0.037] p=0.39	0.026 [-0.076, 0.14] p=0.62	-0.014 [-0.64, 0.039] p=0.60

BOLD = p<0.05, *Italics* = trend for significance

HIV-B participants had significant reductions in grey matter compared to HIV- controls in the United States (US). In South Africa, HIV-C has significant reductions in grey matter, corpus callosum, white matter, thalamus, and hippocampus compared to HIV- controls. No significant clade effects were seen. Overall, HIV+ participants had significant reductions in grey matter, corpus callosum, white matter, thalamus, and hippocampus compared to HIV- controls.