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The effect of central nervous system penetration effectiveness of highly active antiretroviral therapy on neuropsychological performance and neuroimaging in HIV infected individuals

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Abstract

The incidence of HIV-associated dementia has been greatly reduced in the era of highly active antiretroviral therapy (HAART); however milder forms of cognitive impairment persist. It remains uncertain whether HAART regimens with a high degree of central nervous system penetration effectiveness (CPE) exert beneficial neurological outcomes in HIV-infected (HIV+) individuals on stable treatment. Sixty-four HIV-infected adults on HAART were assigned a CPE score using a published ranking system and divided into high (≥ 7; n=35) and low (< 7; n=29) CPE groups. All participants completed neuropsychological testing in addition to structural neuroimaging. Neuropsychological tests included measures known to be sensitive to HIV with values converted into standardized scores (NPZ-4) based on published normative scores. A semi-automated methodology was utilized to assess brain volumetrics within cortical (grey and white matter) and subcortical (thalamus, caudate, putamen) regions of interest. Analyses assessed NPZ-4 and brain volumetric differences between HIV+ individuals with high and low CPE scores. No significant differences in brain integrity were observed between the two groups. Long-term HAART regimens with a high degree of CPE were not associated with significantly improved neuropsychological or neuroimaging outcomes in HIV+ adults. Results suggest that alternate mechanisms may potentially contribute to better neurological outcomes in the era of HAART.

Keywords

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

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Conflicts of Interest:
None to Declare

Introduction

The success of highly active antiretroviral therapy (HAART) in the clinical management of human immunodeficiency virus (HIV) is unmistakable. HIV infected (HIV+) individuals adherent to HAART exhibit reduced viral load (VL) and increased CD4 cell count (Moretti et al., 1999) resulting in reductions in morbidity and mortality (Valcour, 2012; Palella et al., 1998). Unfortunately HAART does not eradicate the virus and reservoirs remain even among individuals with undetectable plasma VLs (Chun et al., 2010). As such, HIV has evolved into a chronic medical condition characterized by varying degrees of residual symptoms that require long-term treatment.

HIV-associated neurocognitive disorder (HAND) is still observed in HIV+ individuals in the HAART era (Heaton et al., 2004). Prior to HAART, the most severe form of cognitive impairment (i.e., HIV-associated-dementia; HAD) affected up to 10–15% of patients (McArthur et al. 1993). Since the introduction of HAART, the prevalence of HAD has been reduced (~3–5%) (Heaton et al., 2010), but milder forms of cognitive impairment persist (Heaton et al., 2011). Importantly, individuals with milder versions of HAND remain at risk for continued progression of cognitive impairment (Grant et al., 2014). The latter findings highlight the importance of identifying variables associated with poor clinical outcomes among individuals receiving HAART.

The presence of cognitive impairment secondary to HIV despite successful control of viral replication in the periphery has raised questions regarding the degree of penetration of HAART across the blood-brain-barrier into the central nervous system (CNS) (Eisfeld, Reichelt, Evers, & Husstedt, 2013). Methods have been developed to quantify the penetration of each antiretroviral medication such as the CNS penetration effectiveness (CPE) score (Letendre et al., 2008; Letendre et al., 2009). However, the relevance of CPE on brain integrity is unclear as some studies have revealed potential benefits of high CPE HAART regimens (Letendre et al., 2008; Cysique et al., 2009), others have shown no effect (Caniglia et al., 2014), and some have demonstrated potentially adverse effects (McManus et al, 2011; Kahouadji et al., 2013).

Neuroimaging provides a robust non-invasive method for identifying structural changes in brain integrity associated with HIV. This technique may provide valuable insights into the impact of CPE within the brain. Similar to prior neuropsychological studies, the effects of CPE on neuroimaging outcomes have been mixed, with some studies reporting no difference between high and low CPE regimens on brain volumetrics (Hua et al, 2013) and others reporting negative effects of high CPE (Gongvatana et al., 2009). To date, no study has analyzed the relationship between CPE and brain integrity using neuropsychological tests and brain volumetrics. Further, most studies assessing the effects of CPE on cognition have focused on individuals initiating or changing HAART. Studies examining the long-term impact of CPE on brain integrity in individuals on stable HAART regimens are needed.

In the present study we utilized both neuropsychological assessment and brain volumetrics to examine the relationship between CPE and brain integrity among HIV+ adults receiving stable HAART. In particular, we examined neuropsychological performance utilizing a

NPZ-4 score comprised of tests of executive function, learning, verbal fluency, and psychomotor speed in HIV+ individuals with high and low CPE scores. We also examined the relationship between CPE and brain morphometry in both cortical (grey and white matter) and subcortical (thalamus, caudate, putamen) regions of interest (ROI) that are often affected by HIV (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Heaps et al., 2012; Ortega et al., 2013).

Methods

Participants

HIV+ individuals on stable HAART (≥ 3 months) were recruited from the Infectious Disease Clinic at Washington University in St. Louis (WUSTL) or the AIDS Clinical Trials Group at WUSTL. Informed consent was obtained from all individual participants included in the study. Individuals were compensated for their participation. The institutional review board at WUSTL approved the study.

HIV status was confirmed through enzyme-linked immunoassay, Western blot, or polymerase chain reaction. Participants were excluded if they reported a history of head injury with loss of consciousness > 30 minutes, major psychiatric disorders, opportunistic CNS infections, or contraindications for MRI scanning.

Clinical measurements

Plasma CD4 T-cell counts and HIV VL were obtained within 3 months of neuropsychological assessment and neuroimaging. Nadir CD4 T-cell count was recorded as lowest value from either self-report or review of medical records. Duration of infection was recorded based on time since diagnosis (per patient recall and/or evaluation of medical records). All medications prescribed were also recorded at the study visit. A detailed neurological exam was performed on each participant by a board certified neurologist (BMA).

Neuropsychological performance testing

All participants were administered a standard battery of neuropsychological tests. Neuropsychological assessments were completed within 1 week of neuroimaging (usually on the same day). The neuropsychological battery measured learning [(Hopkins Verbal Learning Test-Revised (HVLT-R) Immediate Memory], psychomotor speed (Trail Making Test-A; TMT-A), executive function (Trail Making Test-B; TMT-B), and verbal fluency (Animal Fluency). These tests have been previously utilized to assess cognitive function in HIV+ patients (Robertson et al., 2007). Performance on each neuropsychological test was converted to a standardized score (z-score) based on published normative data with adjustments applied for age and, where available, ethnicity, education, and/or gender (Au et al., 2004; Gladsjo et al., 2009; Norman et al., 2013). A standardized score was aggregated for each domain and a cognitive score was determined (NPZ-4). The particular neuropsychological tests included:

HVLT-R Immediate Memory (Benedict et al., 1998) is a list-learning memory test comprised of 12 nouns drawn equally from three semantic categories. Each participant

is administered three immediate recall trials to learn the words, and the total number of words correctly recalled across all the trials serves as the dependent variable.

TMT-A (Reitan & Davison, 1974) measures psychomotor speed and requires a participant to connect 25 numbered circles in sequential order as quickly as possible without lifting the pen from the paper. Time to completion (in seconds) serves as the dependent variable.

TMT-B (Reitan & Davison, 1974) measures executive function by requiring a participant to sequentially connect 25 circles of numbers and letters in an alternate numerical/alphabetical pattern. The time to completion (in seconds) serves as the dependent variable.

Animal Fluency (Goodglass & Kaplan, 1972) measures verbal fluency by requiring each participant to name as many different animals as they can within 60 seconds. The total number of animals correctly stated within the time limit serves as the dependent variable.

Neuroimaging

All neuroimaging was obtained on the same 3T Siemens Tim Trio whole body MR scanner (Siemens AG, Erlangen Germany) using a 12-channel transmit/receive head coil. Structural volumetric images were acquired in the sagittal plane using a T1-weighted 3-dimensional magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence [time of repetition (TR) = 2400ms, echo time (TE)= 3.16ms, inversion time (TI)= 1000msflip angle = 8 degrees, 162 slices, and voxel size = $1\times1\times1mm^3$]. If excessive movement was observed an additional scan was acquired. Quantification of structural volumes was completed using Freesurfer software suite (v5.1) (Martinos Center, Harvard University, Boston, MA; http://surfer.nmr.mgh.harvard.edu). Brain regions were parcellated into subcortical and cortical ROIs using a surface deformation program (Fischl, Sereno, & Dale, 1999; Desikan et al., 2006; Dale, Fischl, B, & Sereno, 1999). All subject images were aligned into a common atlas (MNI305) (Fischl et al., 2004). ROIs often affected by HIV were evaluated and included: cortical matter, total cortical white matter, thalamus, caudate, and putamen (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Heaps et al., 2012; Ortega et al., 2013). Two trained raters independently confirmed the segmentation of ROIs (MO and JMH) and manually implemented edits when necessary. Each volume was normalized to total intracranial volume using a least square residual regression model (Zatz & Jernigan, 1983).

Statistical Analysis

Primary analysis examined differences in neuropsychological performance and structural brain volumetrics between individuals prescribed high (≥ 7) and low (< 7) CPE regimens (Letendre et al., 2008; Letendre et al., 2009). Potential differences in demographic/viral factors were assessed utilizing independent sample t-tests and chi-squared analyses. Cognition (NPZ-4) between groups was measured using univariate analysis of variance (ANOVA). Multivariate analysis of variance (MANOVA) was used to examine the relationships between CPE and individual test z-scores (HVLT-R, TMT-A and B, Verbal

fluency). Differences in brain volumetrics between the groups were also assessed using MANOVA.

Secondary analyses examined whether CPE score as a continuous variable (range 4 to 9) predicted measures of brain integrity (neuropsychological performance and neuroimaging). A univariate linear model was utilized to determine whether CPE score predicted cognition (NPZ-4). A multivariate linear model was used as follow-up analysis to examine whether CPE score predicted individual neuropsychological test z-scores. In both univariate and multivariate models, CPE score was entered as the predictor, NPZ-4 was entered in the univariate model and individual neuropsychological test z scores were entered separately in the multivariate model. The relationship between brain volumetrics and CPE score was measured using a multivariate linear model in which CPE score was entered as the predictor and separate ROIs were entered as the independent variables.

Results

All individuals were over the age of 18 and had been on HAART for ≥ 3 months. There were no significant differences in demographic variables, viral factors, or immune system indices between groups. The two CPE groups were similar with respect to race, gender, age, education, and viral factors. A majority (74%) of the participants had undetectable current VL (< 20 copies/mL) and 59% had a current CD4 cell count > 500 cells/mm^3. The mean duration of infection for the sample was 8.9 years (Table 1). The ANOVA examining the association between CPE score (high vs. low) and NPZ-4 revealed no significant differences between groups ($p > 0.05$). There were also no significant differences between CPE groups with regard to individual neuropsychological tests (p's > 0.05). The MANOVA examining the relationship between CPE score and brain volumes revealed no significant differences between CPE groups ($p > 0.05$) (Table 2). No significant relationships were observed between CPE (continuous variable) with cognition (NPZ-4) ($p > 0.05$) and individual neuropsychological tests (p's > 0.05). Furthermore, the multivariate linear model examining whether CPE score as a continuous variable predicted brain volumes revealed no significant associations ($p > 0.05$).

Discussion

The present study assessed the association between CPE and brain integrity (neuropsychological performance and brain volumetrics) in HIV+ individuals. To our knowledge, this is the first study investigating the effect of CPE on both neuropsychological performance and brain volumetrics in HIV+ individuals on stable HAART (≥ 3 months). Results of the analyses revealed that higher CPE does not influence neuropsychological performance or brain volumes in regions typically impacted by HIV in individuals on stable treatment. These results suggest that mechanisms other than CPE may be more highly related to cognitive outcome in individuals treated with HAART.

Conclusions regarding the relationship between CPE and brain integrity have been mixed. While some research has revealed significant improvement in neuropsychological outcomes within HIV+ individuals on higher CPE regimens (Letendre et al. 2008; Cysique et al.,

2009; Tozzi et al., 2009), the beneficial effects of CPE appear restricted to HIV+ participants with cognitive impairment at baseline (Cysique et al., 2009) or individuals taking ≥ 3 antiretrovirals (Smurzynski et al., 2011). Other studies of CPE and neuropsychological performance have reported adverse effects with high CPE regimens (Marra et al., 2011). The potential iatrogenic effects of HAART have been attributed to potential mitochondrial toxicity, suggesting high CPE scores lead to poor outcomes (Schweinsburg et al., 2005). Based on these prior findings, high CPE may be most beneficial among individuals initiating treatment or prescribed multiple medications; whereas the benefit of high CPE in chronically treated individuals may be mitigated by treatment-related mitochondrial toxicity, ongoing immune activation, HIV reservoirs, or comorbid factors that influence brain outcomes such as substance use or psychological status (Shikuma et al., 2012).

It is possible that other mechanisms may be more salient predictors of neuropsychological outcomes among individuals on long-term HAART than CPE. A recent area of research has focused on understanding the ability of HAART to suppress HIV within circulating monocytes and brain macrophages. It has been hypothesized that the inability to eradicate this reservoir may cause continued inflammation in the CNS. Shikuma and colleagues (Shikuma et al., 2012) have introduced a monocyte effectiveness (ME) scale based on the ability of HAART to sufficiently suppress the virus within circulating monocytes and brain macrophages. In 139 individuals on HAART, a significant relationship was observed between ME and cognitive outcomes (Shikuma et al., 2012). The authors suggested a combined CPE score and ME may better predict cognitive outcomes than each score independently, highlighting an avenue for future research on cognitive impairment in individuals on HAART.

Conclusions regarding the association between CPE and brain integrity should be tempered by several limitations of the present study. The first limitation is the limited battery of neuropsychological tests. While our assessment sampled performance on four neurocognitive domains, it is possible that an extensive battery utilizing multiple tests within each domain would be more sensitive to impact of CPE. However, prior studies have demonstrated the utility of these particular tests to examine cognition in HIV+ individuals (Robertson et al., 2007; Smurzynski et al., 2011). Furthermore, our data were limited to assessments in HIV+ individuals on stable treatment, and did not include baseline neuropsychological performance in order to evaluate improvement or decline after HAART initiation. Therefore, our findings cannot be used to assess initiation or change in regimens and how these directly impact changes in cognition and brain volumetrics.

Taken together, our findings demonstrate that CPE score is not related to cognitive outcomes or structural brain volumes, including total cortical white matter volume, total cortical grey matter volume, and subcortical volumes among individuals on chronic treatment. Comprehensive longitudinal analyses in a HIV+ cohort before and after HAART initiation are warranted to capture the relative impact of HAART upon brain integrity.

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Table 1

Subject Characteristics

	Total Sample (n=64)	Low CPE (n=29)	High CPE (n= 35)
Age (mean years) (SD)	37.96 (12.92)	376.34 (15.17)	39.31 (10.74)
Education (mean years) (SD)[a]	13.17 (2.37)	13.14 (2.39)	13.20 (2.39)
Sex (% Male)	66	68	63
Ethnicity (C/AA)[b]	15/49	8/21	7/28
CD4 Nadir (median cells/mm^3) (IQR)	227.00 (113,360)	218.50 (110,337)	234.50 (153,405)
Recent CD4 (median cells/mm^3) (IQR)	539.50 (377,797)	495.00 (289,649)	621.00 (449,869)
Plasma Viral Load (median copies/mL)[c] (IQR)	1.30 (1.30,1.32)	1.30 (1.30,1.56)	1.30 (1.30,1.30)
Duration of Infection (median months) (SD)	74.50 (39,167)	51.00 (22,164)	99.00 (48,190)

[a] Education based on mean number of years completed

[b] C= Caucasian, AA= African American, A= Asian

[c] Viral load $\log_{10}$ transformed

SD= standard deviation; IQR= interquartile range

Table 2

Effect of CPE score on neuropsychological performance and select ROIs

	Low CPE (n=29) Mean (SD)	High CPE (n= 35) Mean (SD)	*p value*
Neuropsychological Z (NPZ)-scores			
NPZ-4	−.61 (.68)	−.59 (.65)	.89
HVLT-R Immediate Recall	−1.33 (.75)	−1.23 (.83)	.63
TMT-A	−.44 (1.40)	−.41 (1.29)	.92
TMT-B	−.67 (1.37)	−.93 (1.53)	.48
Animal Fluency	−.02 (.90)	.21 (.79)	.29
Structural Brain Volumetrics (adjusted ROI volumes)			
Whole Brain Grey Matter (mm^3)	607014 (52402)	613056 (53049)	.64
Whole Brain White Matter (mm^3)	464299 (34375)	467574 (61315)	.79
Thalamus (mm^3)	13404 (1504)	13636 (1785)	.57
Caudate (mm^3)	7109 (905)	7011 (865)	.65
Putamen (mm^3)	10715 (1267)	10760 (1510)	.82

HVLT-R- Hopkins Verbal Learning Test-Revised; TMT-A-Trail Making Test-A; TMT-B-Trail Making Test-B