The Impact of Central Nervous System Penetration Effectiveness of Highly Active Antiretroviral Therapy on Brain Integrity in HIV+ Adults

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Background

• Highly active antiretroviral therapy (HAART) reduces morbidity and mortality due to human immunodeficiency virus (HIV)/p; however, HAART does not eradicate the virus and reservoirs remain even among individuals with undetectable plasma VL.
• As such, HIV has evolved into a chronic medical condition characterized by varying degrees of residual symptoms that require long-term treatment.
• 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.
• The relevance of CPE on brain integrity is unclear as some studies have revealed potential benefits of high CPE HAART regimens, while others have shown no effect1-3, and some have demonstrated potentially adverse effects.4-5
• Furthermore, HIV-associated neurocognitive disorder (HAND) is still observed in HIV+ individuals.6-8 Prior to HAART, the most severe form of cognitive impairment (i.e., HIV-associated-dementia, HAD) affected up to 10-15% of patients.9 Since the introduction of HAART, the prevalence of HAD has been reduced (3-5%), but milder forms of cognitive impairment persist.10-11 Important, individuals with milder versions of HAD remain at risk for continued progression of cognitive impairment.12-20
• These findings highlight the importance of identifying variables associated with poor clinical outcomes among individuals receiving HAART.

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.
• Participants were excluded if they reported a history of head injury with loss of consciousness over 30 minutes, major psychiatric disorders, opportunistic CNS infections, or (HIV+) individuals on stable treatment.

Neuropsychological Performance

• Neuropsychological tests included measures known to be sensitive to HIV with values converted into standardized scores (z scores) based on published normative scores.
• A standardized score was aggregated for each domain and a cognitive score was determined for future research on cognitive impairment in individuals on HAART.

Statistical Analysis

• Primary Analysis

• Examined differences in neuropsychological performance and structural brain volumetries between individuals prescribed high (≥7) and low (≤4) CPE regimens.5,6
• 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 scores (HVTLR, TMT-A, and RF Ankle length).
• Differences in brain volumetries between the groups were also assessed using MANOVA.

• Secondary Analysis

• Examined the relationship between measures of brain integrity (neuropsychological performance and neuroimaging) and total CPE score as a continuous variable.
• The association between NPZ-4 score and CPE score was measured utilizing linear regression analysis.
• Multiple linear regression was used to examine the relationships between CPE and individual test z-scores.
• The relationship between brain volumetries and CPE score was also measured using multiple linear regression.

Results

• Primary Analysis

• The ANOVA examining the impact of CPE score (high vs. low) on NPZ-4 revealed no significant differences between groups (p > 0.05).
• There were also no significant differences between CPE groups on individual neuropsychological tests (p > 0.05).
• The MANOVA examining the impact of CPE score on brain volumes revealed no significant differences between CPE groups (p > 0.05).

• Secondary Analysis

• No significant relationships were observed between CPE (continuous variable) with cognition (NPZ-4) (p > 0.05) and individual neuropsychological tests (p > 0.05).
• Multiple linear regression model examining the effect of CPE score as a continuous variable on multiple brain volumes revealed no significant associations (p > 0.05).

Conclusions

• 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.
• It is possible that other mechanisms may be more salient predictors of brain integrity 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.
• Shikuma and colleagues have introduced a monocyte effectiveness (ME) scale based on the ability of HAART to sufficiently suppress the virus within circulating monocytes and brain macrophages.21 The authors suggested a means to capture cognitive outcomes than each score independently,21 highlighting an avenue for future research on cognitive impairment in individuals on HAART.
• Comprehensive longitudinal analyses in a HIV+ cohort before and after HAART initiation using CPE and ME scores are warranted to capture the relative impact of HAART upon brain integrity.

Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total Sample (N=64)</th>
<th>Low CPE (n=29)</th>
<th>High CPE (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (SD)</td>
<td>37.97 (12.92)</td>
<td>36.34 (15.18)</td>
<td>39.31 (10.74)</td>
</tr>
<tr>
<td>Education (years) (SD)</td>
<td>13.17 (2.37)</td>
<td>13.14 (2.34)</td>
<td>13.20 (2.40)</td>
</tr>
<tr>
<td>Sex (% Male)</td>
<td>77%</td>
<td>69%</td>
<td>63%</td>
</tr>
<tr>
<td>Ethnicity (C/A/A/A)</td>
<td>15/49/0/0</td>
<td>20/0/0/0</td>
<td>7/28/0/0</td>
</tr>
<tr>
<td>CD4 Nadir (cells/mm3) (IQR)</td>
<td>255.6 (113.35, 360.25)</td>
<td>218.46 (110.75, 337.25)</td>
<td>273.47 (153.25, 405.25)</td>
</tr>
<tr>
<td>Recent CD4 (cells/mm3) (IQR)</td>
<td>553.9 (376.75, 797.00)</td>
<td>510.57 (288.75, 649.25)</td>
<td>639.03 (449.00, 868.50)</td>
</tr>
<tr>
<td>Plasma VL (copies/mL) (IQR)</td>
<td>1.7 (1.30, 1.32)</td>
<td>1.82 (1.30, 1.56)</td>
<td>1.57 (1.30, 1.30)</td>
</tr>
<tr>
<td>Duration of infection (months) (SD)</td>
<td>107.68 (88.01)</td>
<td>89.04 (86.01)</td>
<td>122.05 (88.03)</td>
</tr>
</tbody>
</table>

• Education based on number of years completed. N= Caucasian, AA= African American, A= Asian;
• Viral load log10 transformed, SD= standard deviation, IQR= interquartile range

Table 2. Effect of CPE score on neuropsychological performance and select ROIs

<table>
<thead>
<tr>
<th>Structural Brain Volumes</th>
<th>Low CPE (n=29)</th>
<th>High CPE (n=35)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neocortex</td>
<td>-0.61 (-0.70)</td>
<td>-0.59 (-0.60)</td>
<td>0.89</td>
</tr>
<tr>
<td>HVTLR Immediate Recall</td>
<td>-1.33 (-0.80)</td>
<td>-1.23 (-0.80)</td>
<td>0.63</td>
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<tr>
<td>TMT-A</td>
<td>-0.61 (-1.40)</td>
<td>-0.59 (-1.30)</td>
<td>0.49</td>
</tr>
<tr>
<td>TMT-B</td>
<td>-0.67 (-1.40)</td>
<td>-0.65 (-1.30)</td>
<td>0.48</td>
</tr>
<tr>
<td>Animal Fluency</td>
<td>-0.02 (-0.90)</td>
<td>-0.21 (-0.80)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Acknowledgements

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