Association of Brain Structure Changes and Cognitive Function With Combination Antiretroviral Therapy in HIV-Positive Individuals

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IMPORANCE Despite the introduction of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorders continue to be a problem for treated HIV-positive individuals. The cause of this impairment remains unclear.

OBJECTIVE To determine if detectable brain changes occur during a 2-year period in HIV-positive individuals who were aviremic and treated with cART.

DESIGN, SETTING, AND PARTICIPANTS In this longitudinal case-control study, participants underwent neuroimaging and neuropsychological assessment approximately 2 years apart. Data were collected from October 26, 2011, to March 1, 2016. Data from 92 HIV-positive individuals were acquired at Washington University in St Louis from ongoing studies conducted in the infectious disease clinic and AIDS Clinical Trial Unit. A total of 55 HIV-negative control participants were recruited from the St Louis community and a research participant registry. A total of 48 HIV-positive individuals who were aviremic and treated with cART and 31 demographically similar HIV-negative controls met the study requirements and were included in the analyses.

MAIN OUTCOMES AND MEASURES Brain volumes were extracted with tensor-based and voxel-based morphometry and cortical modeling. Raw scores from neuropsychological tests quantified cognitive performance. Multivariable mixed-effects models assessed the effect of HIV serostatus on brain volumes and cognitive performance, and determined if HIV serostatus affected how these measures changed over time. With HIV-positive participants, linear regression models tested whether brain volumes and cognitive performance were associated with measures of infection severity and duration of infection.

RESULTS The 2 groups were demographically similar (HIV-positive group: 23 women and 25 men; mean [SD] age, 47.7 [13.2] years; mean [SD] educational level, 13.3 [3.4] years; and HIV-negative group, 16 women and 15 men; mean [SD] age, 51.2 [12.9] years; mean [SD] educational level, 14.5 [2.1] years). The HIV-positive participants had poorer neuropsychological test scores compared with controls on the Trail Making Test Part A (5.9 seconds; 95% CI, 1.5-10.3; P = .01), Trail Making Test Part B (27.3 seconds; 95% CI, 15.0-39.6; P < .001), Digit Symbol Substitution Task (~12.5 marks; 95% CI, -18.9 to -6.0; P < .001), Letter-Number Sequencing (~2.5 marks; 95% CI, -3.7 to -1.3; P < .001), Letter Fluency (~6.6 words; 95% CI, -11.5 to -1.6; P = .01), and Hopkins Verbal Learning Test–Revised immediate recall (~2.4 words; 95% CI, -4.4 to -0.4; P = .05), after adjusting for age, sex, and educational level. Only changes in Trail Making Test Part A significantly differed between the groups. Cortical thickness and subcortical volumes were smaller in HIV-positive individuals compared with controls. However, changes in brain volume over time were similar between the groups.

CONCLUSIONS AND RELEVANCE These findings are consistent with the idea that cognitive and structural brain changes may occur early after seroconversion, and argue that maintaining aviremia with cART can prevent or minimize progressive brain injury.
The introduction of combination antiretroviral therapy (cART) has transformed HIV from a fatal disease to a chronic condition. However, HIV-associated neurocognitive disorders (HAND) are still prevalent, affecting up to 40% of HIV-positive individuals despite effective viral suppression.\(^1\) The possible cause of this mild brain dysfunction that limits quality of life remains unclear.

Recently, some studies have reported that, while HAND remains common, progressive worsening is uncommon, with only a small proportion of HIV-positive individuals whose treatment is stable with good viral suppression showing cognitive decline as assessed with repeated neuropsychological testing during a 3- to 4-year period.\(^2-5\) However, it is unclear whether effective viral suppression can mitigate the progression of brain atrophy. Previous neuroimaging studies have provided evidence for ongoing brain atrophy in HIV-positive individuals with advanced disease and poor viral control.\(^6,8\) but those results may not generalize to individuals treated with cART who have viral suppression. A recent neuroimaging study reported no longitudinal changes in cortical thickness, deep gray matter volumes, or white matter integrity in HIV-positive individuals treated with cART who had undetectable viral loads during a 2-year period.\(^9\) However, this study included only 21 participants, had no HIV-negative comparison group, and extracted brain measures only from predefined regions of interest.

In this longitudinal study, we sought evidence of ongoing brain atrophy during a 2-year period using structural magnetic resonance imaging (MRI) and neuropsychological assessment in a larger sample of HIV-positive individuals treated with cART who had well-controlled viral loads, compared with demographically similar HIV-negative controls. We characterized brain volumes as seen on MRI scans by applying multiple advanced neuroimaging processing methods (tensor-based morphometry [TBM], voxel-based morphometry [VBM], and cortical modeling) and assessed cognitive function with a standard battery of neuropsychological tests.

**Methods**

**Participants**

The HIV-positive participants were selected from ongoing studies conducted in the infectious disease clinic and the AIDS Clinical Trial Unit at Washington University in St Louis from October 26, 2011, to March 1, 2016. Demographically similar HIV-negative control participants were recruited from the St Louis community by leaflets and a research participant registry at Washington University in St Louis. Participants were not eligible to enter the studies at Washington University in St Louis if they had a history of confounding neurologic disorders, current or past opportunistic central nervous system infection, traumatic brain injury (loss of consciousness >30 minutes), major psychiatric disorders, or an active substance abuse and dependence diagnosis according to Diagnostic and Statistical Manual of Mental Disorders (fourth edition) criteria. The present study included HIV-positive and HIV-negative participants who had completed 2 MRI and neuropsychological testing sessions at least 1.5 years apart. The HIV-positive participants were receiving stable cART and had undetectable viral loads (<50 copies/mL) at baseline and follow-up visits. Participants were excluded if they had extensive white matter hyperintensities on T2-weighted MRI scans as defined by an expert neurologist (B.M.A.). All participants who met these criteria were included in the analysis, yielding 48 HIV-positive and 31 HIV-negative participants. A CONSORT diagram showing the participant selection process is provided in Figure 1. For all HIV-positive participants, a central nervous system penetration effectiveness (CPE) score was generated based on previous methods.\(^10\) The Washington University in St Louis institutional review board approved the study. Written informed consent was obtained from all participants.

**Neuropsychological Testing**

All participants underwent a neuropsychological assessment at both visits that consisted of 8 standard tests recommended to assess HAND.\(^11\) Trail Making Test Part A and B, Digit Symbol Substitution Task, Letter-Number Sequencing, Letter Fluency, Action (verb naming) Fluency, and Hopkins Verbal Learning Test–Revised immediate and delayed recall. All participants also completed the Wide Range Achievement Test reading subtest to estimate premorbid intellectual ability.\(^12\) Functional limitation in activities of daily living was not assessed.

**MRI Acquisition**

All participants at both visits underwent MRI using the same 3-T Siemens Tim TRIO whole-body magnetic resonance scanner (Siemens) with a 12-channel transmit and receive head coil at Washington University in St Louis. The scanning protocol included T1-weighted 3-dimensional magnetization-prepared rapid acquisition gradient echo sequence (repetition time [TR]/echo time [TE]/inversion time [TI] = 2400/3.16/1000 milliseconds; voxel = 1.0 mm\(^3\)) and T2-weighted Fast Spin Echo sequence (TR/TE = 3200/460 milliseconds; voxel = 1.0 mm\(^3\)).

**MRI Processing**

T1-weighted data were processed using a longitudinal pipeline, as previously described.\(^13\) Preprocessing included denoising,\(^14\) intensity inhomogeneity removal,\(^15\) and brain masking.\(^16\) Images were linearly registered to the Montreal Neurological Institute.
Potentially eligible participants (92 HIV-positive and 55 HIV-negative) enrolled in ongoing studies at WUSTL

147

Excluded (35 HIV-positive and 21 HIV-negative)

56

Did not complete 2 MRI and neuropsychological test sessions (34 HIV-positive and 21 HIV-negative)

55

Did not have undetectable viral loads at both visits (HIV-positive)

1

Without white matter hyperintensities on T2-weighted MRI scans (8 HIV-positive and 3 HIV-negative)

12

Excluded (9 HIV-positive and 3 HIV-negative)

11

Deaths at both visits (HIV-positive)

1

Missing data (HIV-positive)

79

Included for analysis (48 HIV-positive and 31 HIV-negative)

Figure 1. Study CONSORT Diagram

MRI indicates magnetic resonance imaging; and WUSTL, Washington University in St Louis.

International Consortium for Brain Mapping (ICBM) 152 template using a 9-parameter affine transform to correct for variations in head size and orientation. To ensure the registrations to the ICBM152 space were consistent across all time points, a participant-specific template was created using an unbiased template creation approach. This participant-specific template creation process yields nonlinear transformations that maps each visit to the ICBM152 space in a consistent manner reducing the intra-participant variability in brain volume measures across visits, increasing the statistical power to detect changes within participants. All data were carefully inspected for unacceptable processing outcomes. All data passed visual quality control, and were available for TBM, VBM, and cortical modeling.

Tensor-Based Morphometry

Tensor-based morphometry provides a voxelwise estimate of brain structure volume relative to the ICBM152 template. Structural volumes were calculated by taking the Jacobian determinant of the deformation field from the nonlinear transform.

Voxel-Based Morphometry

Voxel-based morphometry provides a voxelwise estimate of the amount of gray matter, white matter, and cerebrospinal fluid. After spatial normalization to the ICBM152 space, each voxel was identified as gray matter, white matter, or cerebrospinal fluid. The tissue maps were then modulated by the Jacobian determinants of the nonlinear transform. Resulting modulated tissue maps were smoothed with an 8-mm full width at half maximum gaussian kernel.

Cortical Modeling

Cortical modeling provides a quantitative measure of cortical thickness. Cortical thickness estimates were extracted with fast accurate cortical extraction by deforming polygonal meshes to fit the gray-white matter and pial surface boundaries.

Thickness estimates were mapped to the ICBM152 mean cortical template using an iterative feature-based registration algorithm and blurred with a 20-mm surface-based kernel.

Statistical Analysis

Multivariable mixed-effects models were used to assess neurocognitive test performance, while voxelwise and vertexwise mixed-effects models were used to assess regional brain volumes, estimated with TBM, VBM, and cortical modeling, from all available data at both visits. To compare neurocognitive scores and brain volumes by HIV serostatus, and to determine if changes in these measures during a 2-year period were significantly different between the HIV-positive and HIV-negative groups, a mixed-effects model included fixed effects for HIV serostatus, time (years from baseline visit), mean age (mean of age at baseline and follow-up), sex, and HIV serostatus by time interaction, as well as a participant-specific random intercept. Within each group, independent mixed-effects frameworks modeled time, age, and sex as fixed effects, along with participant-specific random intercepts, to test if significant changes in test scores and brain volumes occurred between visits. Within the HIV-positive group, linear regressions were used to explore the association between neurocognitive scores and brain volumes with the following HIV-related factors: current and nadir CD4 cell counts, CPE score, and duration of infection. These models were applied to only baseline data. Additional linear regressions tested whether baseline current CD4 cell counts and CPE score were associated with neurocognitive scores and brain volumes at follow-up. Statistical significance was set at P < .05 (2-sided) for all models that assessed neurocognitive performance. Whole-brain statistical maps were corrected for multiple comparisons using the standard false discovery rate with a false-positive rate of 5%. Additional information on model structures can be found in the eAppendix in the Supplement.

Results

Participants

Table 1 summarizes the baseline demographic and clinical characteristics of study participants. The HIV-positive and HIV-negative participants were comparable with respect to age, sex, educational level, race/ethnicity, and history of drug use. The HIV-positive group tended to have lower Wide Range Achievement Test reading scores compared with HIV-negative controls, although these differences did not reach statistical significance after controlling for age, sex, and educational level (raw score, -2.4; 95% CI, -3.9 to -0.9; P = .09). Both groups had similar mean (SD) time periods between visits (HIV-positive, 2.1[0.08] years; HIV-negative, 1.9[0.3] years). All HIV-positive participants were receiving stable cART throughout the study period.

Neuropsychological Performance

The HIV-positive participants had lower neuropsychological scores compared with HIV-negative participants on the Trail Making Test Part A (5.9 seconds; 95% CI, 1.5-10.3; P = .01), Trail
Brain Structure and Cognitive Function in Treated HIV-Positive Individuals

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-Positive Participants (n = 48)</th>
<th>HIV-Negative Participants (n = 31)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>47.7 (13.2)</td>
<td>51.2 (12.9)</td>
<td>.25</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>25 (52)</td>
<td>15 (48)</td>
<td>.93</td>
</tr>
<tr>
<td>Race/ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>15 (31)</td>
<td>16 (52)</td>
<td>.12</td>
</tr>
<tr>
<td>African American</td>
<td>33 (69)</td>
<td>15 (48)</td>
<td></td>
</tr>
<tr>
<td>Educational level, mean (SD), y</td>
<td>13.3 (3.4)</td>
<td>14.5 (2.1)</td>
<td>.09</td>
</tr>
<tr>
<td>WRAT-3 reading score, mean (SD)</td>
<td>43.8 (8.9)</td>
<td>48.1 (6.1)</td>
<td>.09*</td>
</tr>
<tr>
<td>Current CD4 count, median (IQR), cells/µL</td>
<td>630 (486, 881)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Nadir CD4 count, median (IQR), cells/µL</td>
<td>190 (57-300)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Estimated duration of HIV infection, median (IQR), y&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.5 (5.2-20)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C coinfection, No. (%)</td>
<td>1 (2)</td>
<td>0</td>
<td>.30</td>
</tr>
<tr>
<td>CPE score, median (range)</td>
<td>7.5 (5-13)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Past substance use, No. (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marijuana</td>
<td>5 (10)</td>
<td>3 (10)</td>
<td>.90</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>.80</td>
</tr>
<tr>
<td>Opiates</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>.80</td>
</tr>
</tbody>
</table>

Abbreviations: CPE, Central Nervous System Penetration Effectiveness; IQR, interquartile range; NA, not applicable; WRAT-3, Wide Range Achievement Test.

Table 2. Neuropsychological Test Scores at Baseline and Follow-up

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>HIV-Positive Participants</th>
<th>P Value for Change Over Time&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HIV-Negative Participants</th>
<th>P Value for Change Over Time&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value for Group Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail Making Test A, time to completion, s&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32.5 (11.0)</td>
<td>.08</td>
<td>26.0 (7.6)</td>
<td>.14</td>
<td>.01</td>
</tr>
<tr>
<td>Trail Making Test B, time to completion, s&lt;sup&gt;b&lt;/sup&gt;</td>
<td>93.7 (38.0)</td>
<td>.21</td>
<td>63.2 (16.4)</td>
<td>.20</td>
<td>.04</td>
</tr>
<tr>
<td>HVLT-R: immediate recall, No. of correct words&lt;sup&gt;c&lt;/sup&gt;</td>
<td>20.8 (4.7)</td>
<td>.29</td>
<td>23.4 (4.7)</td>
<td>.30</td>
<td>.05</td>
</tr>
<tr>
<td>HVLT-R: delayed recall, No. of correct words&lt;sup&gt;c&lt;/sup&gt;</td>
<td>7.5 (2.4)</td>
<td>.60</td>
<td>8.5 (3.1)</td>
<td>.43</td>
<td>.24</td>
</tr>
<tr>
<td>Digit Symbol Substitution Task, No. of correct marks&lt;sup&gt;c&lt;/sup&gt;</td>
<td>65.3 (15.3)</td>
<td>.02</td>
<td>76.6 (15.9)</td>
<td>.73</td>
<td>.01</td>
</tr>
<tr>
<td>Letter-Number Sequencing, No. of correct marks&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.3 (3.2)</td>
<td>.70</td>
<td>10.9 (2.7)</td>
<td>.78</td>
<td>.001</td>
</tr>
<tr>
<td>Action Fluency, No. of verbs&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12.6 (4.9)</td>
<td>.74</td>
<td>15.6 (7.4)</td>
<td>.21</td>
<td>.10</td>
</tr>
<tr>
<td>Letter Fluency, No. of words&lt;sup&gt;c&lt;/sup&gt;</td>
<td>33.4 (11.2)</td>
<td>.003</td>
<td>40.1 (12.7)</td>
<td>.02</td>
<td>.01</td>
</tr>
</tbody>
</table>


Making Test Part B (27.3 seconds; 95% CI, 15.0-39.6; P < .001), Digit Symbol Substitution Task (-12.5 marks; 95% CI, -18.9 to -6.0; P < .001), Letter-Number Sequencing (-2.5 marks; 95% CI, -3.7 to -1.3; P < .001), Letter Fluency (-6.6 words; 95% CI, -11.5 to -1.6; P = .01), and Hopkins Verbal Learning Test-Revised immediate recall (-2.4 words; 95% CI, -4.4 to -0.4; P = .05), after adjusting for age, sex, and educational level with mixed-effects modeling. Participant level intercept was included as a random effect. P value derived from likelihood ratio testing.

Table 2. Neuropsychological Test Scores at Baseline and Follow-up

The primary analysis compared changes in neuropsychological scores over time by HIV serostatus. Improvements in test scores were observed in Letter Fluency in HIV-positive (1.4 words per year; 95% CI, 0.5-2.3; P = .003) and HIV-negative participants (1.7 words per year; 95% CI, 0.2-3.3; P = .02) and Digit Symbol Substitution Task in the HIV-positive group (1.1 marks per year; 95% CI, 0.3-2.0; P = .02). Differences in Trail Making Part A scores differed between the groups (-1.9 seconds per year; 95% CI, -3.8 to -0.02; P = .03): the HIV-positive group had greater improvements compared with HIV-negative individuals over time. No significant interactions between HIV serostatus and time were detected in other neuropsychological test results.

Neuropsychological scores did not correlate with current CD4 count, nadir CD4 count, CPE score, or duration of infection. In addition, baseline current CD4 and CPE scores did not predict neuropsychological performance at follow-up.

Brain Volumes

Comparing brain volumes revealed reduced cortical thickness and smaller subcortical volumes in the HIV-positive group compared with controls (Figure 2; eFigure 1 in the Supplement). Cortical thickness differences were detected in the bilateral primary sensory and motor cortex, superior tempo-
ral gyrus and poles, middle and posterior cingulate cortex, and left frontal lobe (Figure 2A). Tensor-based morphometry revealed significantly smaller subcortical volumes, and VBM showed significantly reduced white matter volumes in the thalamus, caudate, putamen, globus pallidus, brainstem, and midbrain of HIV-positive participants (Figure 2B). Modeling brain volumes over time did not reveal significant differences in the changes in regional volume or cortical thickness between the groups. The changes in these brain volume estimates over time were similar between the groups.

Power calculations were performed to aid in interpreting the absence of detectable differences in brain volume change. This analysis showed that differences in loss of brain volume between the groups ranging from 0.1% to 6.0% per year (median, 0.90% per year [interquartile range, 0.71%-1.12%]) could have been detected, if present, when brain volumes were estimated with TBM or VBM (eFigure 2 in the Supplement). Likewise, differences in cortical thickness changes between groups ranging from 0.01 to 0.5 mm per year (median, 0.08 mm per year [interquartile range, 0.07-0.1]) could have been detected, if present, using cortical modeling (eFigure 3 in the Supplement).

Lower nadir CD4 counts were significantly correlated with reduced white matter volumes and smaller brain volumes in the putamen, globus pallidus, and thalamus, as revealed with VBM.
and TBM (Figure 3). In contrast, no correlations between nadir CD4 counts and cortical thickness estimates were observed. The remaining HIV-associated factors (current CD4 count, CPE score, and duration of infection) were not associated with any brain volume estimates. Baseline current CD4 count and CPE score was not significantly associated with brain volumes at follow-up.

Discussion

Although HAND persists, recent studies have reported that neuropsychological performance does not deteriorate during durations of 3 to 4 years in most HIV-positive individuals who were aviremic and treated with cART. Whether stable treatment and effective viral suppression also prevents progressive structural brain atrophy is unclear. We observed significant differences in cortical thickness, subcortical volumes, and cognitive performance in HIV-positive participants compared with demographically similar HIV-negative controls at both visits. However, the changes in cognition and brain volumes during the 2-year period were similar between the HIV-positive and HIV-negative groups.

We applied multiple neuroimaging processing methods capable of detecting small changes in cortical thickness and subcortical volumes. Post hoc power analysis demonstrated that differences in annual loss of brain volume between the groups as small as 0.1% per year in subcortical regions and 0.01 mm per year in the cortex could be detected, if present. Changes of greater magnitude were reported in an HIV-positive group, 33% of whom had detectable viral loads, with 3.2% more volume loss detected in the temporal lobe compared with an HIV-negative group. In other conditions with mild cognitive impairment, such as prion disease, thining rates were 0.01 mm per year greater in individuals who progressed to mild cognitive impairment compared with those who maintained cognitive health. Although the absence of detectable cortical thinning and subcortical volume loss in our study is not proof of the absence of ongoing brain atrophy in HIV-positive individuals, the power analysis demonstrates that clinically meaningful changes could have been detected, if present. These findings are consistent with those of a recent smaller longitudinal study, which likewise found no significant changes in mean cortical thickness and deep gray matter volumes during a 2-year period in HIV-positive participants with undetectable viral loads receiving treatment with cART. Collectively, these findings support the hypothesis that effective viral suppression with stable cART could halt the previously reported progression of brain atrophy in HIV.

Improvements in neuropsychological test scores were observed to a similar degree in both groups in the Letter Fluency and Digit Symbol Substitution tasks. Improvement was also seen in Trail Making Test Part A scores, with the HIV-positive group showing greater improvements than controls. On average, these improvements were less than 0.5 SD from baseline, a threshold generally considered to indicate clinically meaningful change. The observed improvements in test scores likely reflect imperfect test-retest reliability and practice effects; in any case, the findings argue against substantial cognitive decline. However, a caveat of mixed-effects modeling is the assumption that patterns of longitudinal change are the same for all individuals, which may not be true. It is possible that the mixed-effects models masked unique cognitive trajectories that have clinical meaning. Future studies should consider alternative approaches such as group-based trajectory analysis, which identifies distinct cognitive trajectories. This approach was applied to a large sample of HIV-positive participants drawn from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort. Consistent with our findings, a decline in scores of even one neuropsychological test was uncommon, with most HIV-positive participants remaining cognitively stable during a 3-year period.

The absence of worsening cognitive function also agrees with a recent Multicenter AIDS Cohort study and another CHARTER study. These studies found that stability was the rule, with only small subsets of HIV-positive participants having deterioration in neuropsychological performance or HAND status. Those studies supported the possibility that cardiovascular disease contributed to cognitive decline, with lower high-density lipoprotein concentrations and hypercholesterolemia predicting decline. We focused on individuals who were aviremic and treated with cART, excluding those with evidence of white matter hyperintensities attributable to microvascular injury a priori, to test the hypothesis that HIV, rather than vascular comorbidities, causes brain injury. Future studies should evaluate brain volumes and neuropsychological performance in HIV-positive individuals over a longer period to clarify whether very subtle progressive effects continue. Studies specifically concentrating on older HIV-positive individuals (>55 years) are also needed, as increasing age and HIV infection may have synergistic effects on brain structure and function.

Smaller cortical and subcortical volumes and poorer cognitive performance in the HIV-positive group may reflect brain injury that occurred soon after seroconversion, possibly during the time of untreated infection. Viral markers and markers of immune activation are elevated in the cerebrospinal fluid during this phase of the infection. These viral and immunopathogenic changes are thought to be associated with neuronal damage. If the infection is left untreated, high levels of HIV replication continue, leading to increased production of toxic viral proteins and proinflammatory responses, resulting in potentially permanent damage. Supporting this hypothesis, cross-sectional studies
investigating brain volumes and cognitive function in primary HIV infection (defined as <1 year after exposure) have reported reduced putamen and cortical gray matter volumes, and poorer cognitive performance in tasks involving executive function, attention and working memory, language, and speed of information processing. This finding demonstrates that neuronal injury is present early in the infection. Our results are also consistent with a large body of cross-sectional work with individuals with chronic HIV infection (defined as >1 year after exposure) who reported volume reductions throughout the subcortical regions, cortical thickness reductions in the primary sensory and motor cortices, temporal lobe, and middle cingulate cortex; and weaker performance on neuropsychological tests compared with controls.

Supporting the idea that these differences are associated with events prior to initiation of cART, previous studies have demonstrated that a history of more severe immunosuppression, indexed by nadir CD4 cell counts, is associated with smaller brain volumes and poorer neuropsychological performance. We observed a significant correlation between lower nadir CD4 counts and smaller subcortical volumes, but not with cortical thickness or neuropsychological performance. Although this finding corresponds with previous work, the literature is not consistent because smaller cortical volumes and poorer neuropsychological performance have been previously linked with lower nadir CD4 counts. Discrepancies between the results most likely reflect differences in sample size, disease severity, and neuropsychological test selection. Taken together, our results could support the hypothesis that neurobiological changes occurring early in infection may be responsible for the cognitive impairment found in chronic HIV-positive individuals. This finding suggests that early initiation of cART may have neurocognitive benefits. However, future longitudinal work assessing brain structure and function in primary HIV infection is required to verify this hypothesis.

The effect of treatment central nervous system penetration effectiveness, indexed by CPE score, on brain volumes and neuropsychological test performance was also explored. No correlations with any brain volume measures or neuropsychological test scores were observed. This outcome suggests that treatment regimens with higher penetration do not influence brain structure or function. However, given the limited number of treatment regimens prescribed (CPE score range, 5-13), this sample of HIV-positive participants was not appropriate to demonstrate the potential neuroprotective or neurotoxic effects of cART.

**Limitations**

This study has limitations. First, recent evidence has suggested that cardiovascular risk factors are more common in HIV-positive individuals and are associated with cognitive deficits. Although we excluded participants with overt evidence of cerebrovascular disease on results of imaging, data on vascular risk factors were not acquired. We cannot definitively exclude that vascular injury contributes to the smaller brain volumes and cognitive deficits. Second, this study focused on the direct effects of HIV, by including HIV-positive participants who were aviremic and treated with cART who had minimal comorbidities and no white matter hyperintensities. This selection limits the generalizability to individuals with similar characteristics. Indeed, HIV-positive individuals with lesions or other comorbid conditions may be more likely to experience ongoing brain injury despite full viral suppression. Finally, although the HIV-positive group performed more poorly on neuropsychological tests than the HIV-negative controls, we did not collect information on the functional limitations of daily living needed to categorize participants with respect to the HAND categories; our focus was on the change within the individual over time. The ability to detect change in neuropsychological performance depends on the tests used. It is possible that different tests would yield different results. For example, our neuropsychological assessment did not include measures of nonverbal learning and memory or tests of abstractions. However, no evidence of deterioration on the Trail Making Test Part B were observed, which was demonstrated to be the cognitive test most likely to show decline during a 36-month period across a battery of 15 neuropsychological tests administered to 701 HIV-positive individuals in a longitudinal CHARTER cohort. In that study, as well as ours, improvements in some test scores were observed, presumably owing to practice effects. These effects could yield stable performance despite underlying progressive brain injury, but the absence of detectably poorer brain volume loss in the same HIV-positive sample here argues against this interpretation.

**Conclusions**

We used multiple neuroimaging methods to assess brain structure and cognitive function in a cohort of HIV-positive participants with good virologic control who were treated with cART and demographically similar HIV-negative controls. Although we observed smaller cortical thickness and subcortical volumes and poorer cognitive function in the HIV-positive group, there was no significant brain volume loss or neuropsychological decline during a 2-year period. These findings support the hypothesis that brain injury due to HIV could occur principally during untreated infection. This finding suggests that early initiation of cART and full viral suppression may preserve long-term brain health.


16. Eskildsen SF, Østergaard LR. Active surface approach for extraction of the human cerebral cortex from MRI. Paper presented at: Medical Image Computing and Computer-Assisted Intervention; October 1, 2006; Copenhagen, Denmark.


