Brain MRI changes associated with poorer cognitive function despite suppressive antiretroviral therapy

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Background

Reported prevalence of HIV-associated cognitive impairment remains high

European cohort studies with appropriate HIV-control populations now established

Hypotheses tested

Despite suppressive cART, compared to an appropriate control population, HIV+ individuals will have evidence of:

- Poorer cognitive performance
- Grey and white matter atrophy
- White matter microstructural abnormalities

Structural brain and cognitive abnormalities would occur together and be more common in HIV+ individuals
Participants

Inclusion criteria

HIV+ group (n=134)
• documented HIV infection
• age ≥ 45 years at study entry
• documented plasma HIV RNA <50 copies/mL > 12 months on cART

HIV- group (n=79)
• documented negative HIV test in past 6 months or at screening
• age ≥ 45 years at study entry

Exclusion criteria

• current major depression (PHQ-9 ≥ 15)
• chronic neurological diseases
• history of severe head injury
• history of cerebral infections (including AIDS defining illnesses)
• severe psychiatric disease

All underwent: cognitive testing, MRI scanning (several modalities) and CSF examination (not presented today)
Methods

Cognitive battery
(testing attention, executive function, language, memory, motor function and processing speed)
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(testing attention, executive function, language, memory, motor function and processing speed)

Volumetric

1. Bias correction and segmentation (SPM12)
2. SPM12 (DARTEL)
3. Spatial normalisation

T1 data
(n=212)

Neuroimaging (3T)

1. Data acquisition and pre-processing
2. DTITK
3. 64 direction diffusion weighted data
(n=208)

Diffusion

Segmented
Grey matter
White matter

Fractional anisotropy
Axial diffusivity
Mean diffusivity
Radial diffusivity

\[
\lambda_1 = \text{longitudinal (axial) diffusivity (AD)}
\]
\[
\frac{\lambda_1 + \lambda_2 + \lambda_3}{2} = \text{radial diffusivity (RD)}
\]
\[
\frac{\lambda_1 + \lambda_2 + \lambda_3}{3} = \text{mean diffusivity (MD)}
\]
\[
\sqrt[3]{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2} = \text{fractional anisotropy (FA)}
\]
Statistics

Cognitive battery
(testing attention, executive function, language, memory, motor function and processing speed)

Raw scores converted to demographically adjusted cognitive domain T-scores

Cognitive impairment defined using Frascati\textsuperscript{1}, GDS\textsuperscript{2} and MNC\textsuperscript{3} criteria

Group comparison
(with chi-squared and Wilcoxon rank-sum as appropriate)

\textsuperscript{1}Antinori A et al, Neurology (2007); \textsuperscript{2}Carey CL et al. J Clin Exp Neuropsych (2004); \textsuperscript{3}Huizenga HM et al, Neuropsychologia (2007)
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Group comparison with non-parametric permutation testing (using FSL’s \textit{randomise} 10,000 permutations, adjusted for age, ICV and scanner)

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Statistics

Cognitive battery
(testing attention, executive function, language, memory, motor function and processing speed)

Raw scores converted to demographically adjusted cognitive domain T-scores

Cognitive impairment defined using Frascati¹, GDS² and MNC³ criteria

Group comparison defined using Frascati¹, GDS² and MNC³ criteria

Group comparison defined (with chi-squared and Wilcoxon rank-sum as appropriate)

Extraction of summary statistics using atlases (FSL)

Group comparison with non-parametric permutation testing (using FSL’s randomise 10,000 permutations, adjusted for age, ICV and scanner)

Volumetric

Neuroimaging (3T)

Diffusion

Segmented
Grey matter
White matter
Fractional anisotropy
Axial diffusivity
Mean diffusivity
Radial diffusivity

## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV+ (n=134)</th>
<th>HIV- (n=79)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years), median (IQR)</td>
<td>55 (51-62)</td>
<td>57 (52-64)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Gender</strong>, n (%)</td>
<td></td>
<td></td>
<td>0.79</td>
</tr>
<tr>
<td>Female</td>
<td>9 (7%)</td>
<td>6 (7%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>125 (93%)</td>
<td>73 (92%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong>, n (%)</td>
<td></td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Black-African</td>
<td>16 (12%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>117 (88%)</td>
<td>76 (97%)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexuality</strong>, n (%)</td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>MSM</td>
<td>104 (77%)</td>
<td>59 (75%)</td>
<td></td>
</tr>
<tr>
<td>Bisexual</td>
<td>10 (8%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>18 (13%)</td>
<td>16 (20%)</td>
<td></td>
</tr>
<tr>
<td><strong>Years of education</strong>, median (IQR)</td>
<td>14 (13-16)</td>
<td>16 (14-17)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Smoking status</strong>, n (%)</td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>Current smoker</td>
<td>40 (30%)</td>
<td>20 (25%)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>58 (43%)</td>
<td>29 (37%)</td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>36 (27%)</td>
<td>30 (38%)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol consumption</strong>, n (%)</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Current drinker</td>
<td>104 (78%)</td>
<td>71 (90%)</td>
<td></td>
</tr>
<tr>
<td>Previous drinker</td>
<td>18 (13%)</td>
<td>3 (5%)</td>
<td></td>
</tr>
<tr>
<td>Never drunk</td>
<td>12 (9%)</td>
<td>4 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Use of recreational drugs in past 6 months</strong>, n (%)</td>
<td>44 (33%)</td>
<td>18 (23%)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
### Baseline characteristics — HIV+ group

<table>
<thead>
<tr>
<th>Likely route of HIV transmission, n (%)</th>
<th>n=134</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>115 (86%)</td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>IVDU/Blood product</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2%)</td>
</tr>
<tr>
<td><strong>Years since HIV diagnosis</strong>, median (IQR)</td>
<td>15.0 (9.1-20.0)</td>
</tr>
<tr>
<td><strong>Duration of cART (years)</strong>, median (IQR)</td>
<td>12.5 (7.4-16.9)</td>
</tr>
<tr>
<td><strong>HIV RNA viral load &lt; 200 copies/mL</strong>, n (%)</td>
<td>134 (100%)</td>
</tr>
<tr>
<td><strong>CD4 count (cells/μL)</strong>, median (IQR)</td>
<td>629 (472-806)</td>
</tr>
<tr>
<td><strong>Nadir CD4 count (cells/μL)</strong>, median (IQR)</td>
<td>180 (90-250)</td>
</tr>
<tr>
<td><strong>CD4+:CD8+ cell count ratio</strong>, median (IQR)</td>
<td>0.84 (0.60-1.12)</td>
</tr>
</tbody>
</table>
HIV-positive group has poorer cognitive function

**Global deficit score:**
- 18% vs. 4%
- OR 5.6 (1.9-24.1)

**Frascati criteria:**
- 18% vs. 4%
- OR 5.6 (1.7-24.1)

**Multivariate normative comparison:**
- 20% vs. 3%
- OR 9.4 (2.7-59.2)

*Boxplots of demographically adjusted cognitive domain T-scores by HIV-serostatus.* P values calculated using Wilcoxon rank sum test.
**HIV-associated grey matter atrophy**

**Grey matter voxel based morphometry group comparison.** Areas with significantly (p < 0.05) lower grey matter volume coloured by the t-statistic - corrected for multiple comparisons (TFCE) and adjusted for age, intracranial volume and scanner. Statistical image overlaid on MNI 152 T1
HIV-associated white matter injury

White matter tract based spatial statistics group comparison. Areas of significantly (p < 0.05) lower fractional anisotropy (FA), higher mean diffusivity (MD) and higher radial diffusivity (RD) are coloured by t-statistic red-yellow, light blue and dark blue respectively - corrected for multiple comparisons (TFCE) and adjusted for age, intracranial volume and scanner. Overlaid on the white matter skeleton (green) and the mean FA image (greyscale).
K-means cluster analysis: both groups

Higher GM volume/FA (n=99)  Lower GM volume/FA (n=109)

2 cluster solution optimally partitioned data
• Duda-Hart test: p<0.0001

High degree of stability to resampling
• Jaccard bootstrap mean 0.99 for both clusters

Discriminant coordinate plot showing the separation of the clusters based on the k-means cluster analysis of parcellated grey matter and mean fractional anisotropy data. Each individual number represents a participant with the number representing their cluster assignment.
K-means cluster analysis: HIV-

Higher GM volume/FA (n=47)

Lower GM volume/FA (n=27)

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Higher GMV/FA</th>
<th>Lower GMV/FA</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64%</td>
<td>36%</td>
<td>0.36 (0.20-0.66)</td>
</tr>
</tbody>
</table>

Discriminant coordinate plot showing the separation of the clusters based on the k-means cluster analysis of parcellated grey matter and mean fractional anisotropy data. Each individual number represents a participant with the number representing their cluster assignment.
K-means cluster analysis: HIV+

Higher GM volume/FA (n=52)

Lower GM volume/FA (n=82)

Discriminant coordinate plot showing the separation of the clusters based on the k-means cluster analysis of parcellated grey matter and mean fractional anisotropy data. Each individual number represents a participant with the number representing their cluster assignment.
Imaging phenotype associated with poorer cognitive function

Jitterplot of cognitive domain T-scores grouped by k-means cluster analysis. Black lines represent medians for each cluster with p-values calculated using the Wilcoxon rank sum test.
**Imaging phenotype associated immune activation and older age**

**HIV+ individuals:**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cluster</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Higher GMV/FA</td>
<td>Lower GMV/FA</td>
</tr>
<tr>
<td>Age</td>
<td>53.2</td>
<td>58.6</td>
</tr>
<tr>
<td>CD4:CD8 ratio</td>
<td>1.06</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Note: Cognitive domain T-scores account for age and level of education and groups are matched for age.

**Jitterplot of cognitive domain T-scores grouped by k-means cluster analysis.** Black lines represent medians for each cluster with p-values calculated using the Wilcoxon rank sum test.
Conclusions

HIV+ individuals have evidence of cognitive impairment, grey matter atrophy and white matter microstructural injury
• despite fully suppressive cART
• compared to an appropriate control population

Structural brain abnormalities tend to occur together
• found more commonly in HIV+ individuals
• associated with poorer cognitive function
• associated with markers of immune dysregulation

Limitations – cohort study
• unmeasured differences could confound group comparisons
• but mitigated against this with an appropriate HIV- control group
The Co-morBidity in Relation to Aids (COBRA) Collaboration

Imperial College of Science, Technology and Medicine - Department of Medicine, Division of Infectious Diseases: A. Winston, J. Underwood, L. McDonald, M. Stott, K. Legg, A. Lovell, O. Erlwein, N. Doyle, C. Kingsley. Department of Medicine, Division of Brain Sciences, The Computational, Cognitive & Clinical Neuroimaging Laboratory: D.J. Sharp, R. Leech, J.H. Cole.

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Thank you for listening. Any questions?