Viral Decay Rate in the Cerebrospinal Fluid After Initiating Antiretroviral Therapy


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Introduction
Infection with Human Immunodeficiency Virus (HIV) can be associated with a variety of neurological syndromes that include opportunistic infections and pathology mediated directly by HIV. In the pre-combination antiretroviral therapy (cART) era, HIV-associated dementia (HAD) occurred in 1/3 patients, and HAD and other HIV-associated neurocognitive disorders (HAND) are still prevalent today. The role of viral replication in the central nervous system (CNS) in these syndromes is not well-understood, but cART ameliorates or prevents HAND in most but, crudely, not all HIV-infected patients. Initiation of cART typically results in the rapid decay of HIV-1 in the cerebrospinal fluid (CSF); however, in a subset of HIV-infected people, virus in the CSF decays very slowly despite the use of cART. This persistence may be due to factors related to the pharmacological characteristics of antiretrovirals, to host immune response, to features of the virus, or to compartmentalization of HIV in privileged places like the central nervous system.

Materials and Methods
- Participants in the HIV Tropism, Persistence, Inflammation, and Neurocognition in Therapy Initiation Cohort Study
- Recruited treatment-naive patients with CD4 ≥ 400 starting antiretroviral therapy (ART)
- All participants underwent medical and neurological examination, neuropsychiatric testing, blood draw, and lumbar puncture (LP) at baseline and 2-4 weeks after initiation of ART.
- Measured blood and CSF HIV viral loads (VL), blood CD4 count, and blood and CSF laboratories at each visit. VLs less than 40 were estimated as 20 if undetectable and as exact copy number when detectable.
- Decay rates were calculated as change in log(VL) divided by number of days on ART.
- Pair-wise correlations with Bonferroni correction were used to examine relationships between linear variables
- Student’s t-test, Mann-Whitney U test, Wilcoxon signed-rank and rank sum tests or Kruskal-Wallis test were used to evaluate change in linear variables between visits or groups
- Risk ratios were calculated for clearance of HIV from the CSF
- Multivariate linear regression was used to identify significant variables associated with viral clearance.

Results
We recruited 40 treatment-naive patients, and 30 returned for LP 2 to 4 weeks after initiation of ART and were included in analyses:
- 25 men, 5 women (all drop-outs were men)
- 10 black, 10 white, 1 other; 3 Hispanic
- Median age 35 years (range 21-64)
- Median CD4 count was 257 (range 6-394)
- Median time between visits was 24 days (range 11-129)
- Median time on therapy at second LP was 18 days (range 12-36)
- Median blood VL decay rate = 0.13 log copies/day (range < 0.01–0.22)
- Median CSF VL decay rate = 0.06 log copies/day (range > 0.03–0.17)
- Mean log(CSF VL) declined by 1.24.

Laboratory measurements at baseline and on ART

<table>
<thead>
<tr>
<th>Median CD4 count</th>
<th>% with detectable blood HIV</th>
<th>Median blood HIV load</th>
<th>Mean log(blood VL)</th>
<th>% with detectable CSF HIV</th>
<th>Median CSF viral load</th>
<th>Mean log(CSF VL)</th>
<th>Median CSF WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>257 (6-394)</td>
<td>100%</td>
<td>40470 (168-110665)</td>
<td>4.53 (0.81)</td>
<td>97%</td>
<td>381 (30-1956)</td>
<td>3.09 (1.20)</td>
<td>5 (1.49)</td>
</tr>
</tbody>
</table>

Viral decay stratified by antiretroviral regimen

<table>
<thead>
<tr>
<th>Baseline log-CSF VL</th>
<th>protease inhibitor</th>
<th>NRTI inhibitor</th>
<th>NNRTI inhibitor</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.78</td>
<td>3.62</td>
<td>3.83</td>
<td>2.31</td>
<td>NS</td>
</tr>
<tr>
<td>4.56</td>
<td>4.12</td>
<td>0.09</td>
<td>0.15</td>
<td>0.06 NS</td>
</tr>
<tr>
<td>4.45</td>
<td>4.09</td>
<td>0.07</td>
<td>0.05</td>
<td>0.03 NS</td>
</tr>
<tr>
<td>6.34</td>
<td>4.09</td>
<td>0.07</td>
<td>0.06</td>
<td>0.03 NS</td>
</tr>
<tr>
<td>6.49</td>
<td>3.07</td>
<td>0.18</td>
<td>0.12</td>
<td>0.05 NS</td>
</tr>
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<td>6.34</td>
<td>3.07</td>
<td>0.18</td>
<td>0.12</td>
<td>0.05 NS</td>
</tr>
</tbody>
</table>

Correlation coefficients for linear variables. Coefficients in red p-value ≤ 0.05.

<table>
<thead>
<tr>
<th>log(blood VL) decay rate</th>
<th>log-CSF VL decay rate</th>
<th>Age</th>
<th>time between LPs</th>
<th>Baseline CD4 count</th>
<th>baseline VL</th>
<th>2-week log(blood VL)</th>
<th>2-week log(CSF VL)</th>
<th>baseline CSF VL</th>
<th>2-week CSF VL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.28</td>
<td>0.28</td>
<td>0.8</td>
<td>0.31</td>
<td>0.25</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.48</td>
<td>0.02</td>
<td>0.22</td>
</tr>
<tr>
<td>0.04</td>
<td>0.05</td>
<td>0.5</td>
<td>0.04</td>
<td>0.25</td>
<td>1</td>
<td>0.04</td>
<td>0.05</td>
<td>0.5</td>
<td>0.33</td>
<td>0.03</td>
</tr>
<tr>
<td>0.15</td>
<td>0.15</td>
<td>0.1</td>
<td>0.04</td>
<td>0.25</td>
<td>1</td>
<td>0.15</td>
<td>0.05</td>
<td>0.5</td>
<td>0.33</td>
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Conclusions
HIV viral decay rate in the CNS:
- Treatment-naive HIV positive subjects with CD4 counts ≤ 400, there is a broad range of CSF HIV RNA levels that do not correlate significantly with blood HIV VL.
- Decay rates of HIV RNA appears slower in the CSF than in blood, possibly due to compartmentalization.
- Baseline CSF HIV VL was correlated with CSF WBC.
- In multivariable analysis, only baseline higher CSF VLs and faster blood VL decay rates predicted faster decay of HIV in CSF after initiation of ART.

Effect of antiretroviral regimen:
- Though not significant in multivariable analyses, protease inhibitors were associated with faster CSF viral suppression.
- Integrate inhibitors were associated with slower suppression of HIV in the CNS, though baseline CSF VL was lower in this group.
- These findings were unexpected on prior reports, faster blood VL decay seen with integrate inhibitors, and known CNS penetration of these drug classes.
- These findings need to be confirmed in future studies with much larger sample sizes, ideally in a randomized controlled trial.

Limitations:
- Small numbers – only 30 subjects with complete data.
- Short follow up – will have 1 year data.
- Compartmentalization data not yet available.
- A comparison on treatment follow up measurement may not reflect first and second phase decay, as decay is unlikely to be log-linear over a longer time period.

Literature Cited

Acknowledgments
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