Emerging Considerations in neuroAIDS Internationally: Events in Acute and Early Infection

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Although combination ARVs improve health and prolong survival, neuroAIDS remains prevalent.
Public Health Importance of studies on Acute/Early infection

» There are estimated to be 5,000,000 new cases of HIV worldwide annually (40,000 in USA)
» World wide prevalence is 40,000,000
» As people survive longer, and if we estimate 35% develop HAND, there may be 14,000,000 cases with neurocognitive impairment
» In USA, with about 1,000,000 HIV cases, there may be 350,000 with HAND. This makes HIV the 2\textsuperscript{nd} most important source on cognitive impairment (after traumatic brain injury) among adults in their most productive years
» If HAND can be prevented initially, significant source of morbidity is eliminated, and quality of life improved
Neurocognitive Impairment in CHARTER Cases
Associated with:

» Nadir CD4 < 200 (p = .01)

» ARV (p = .005): current ARV treated worse than those never on ARV (but nadir CD4 < 200 in 74% of currently treated vs. 27% never treated)

» Plasma VL x Nadir CD4 < 200 (p = .006): undetectable VL and nadir CD4 > 200 were less impaired

» No univariate associations to current CD4, plasma or CSF viral load
Reduced Risk of NCI in Those with Absent History of Severe Immunosuppression and Good Virologic Control
Markers of HIV Infection Progression Over Time

- CD4 Lymphocytes
- Plasma HIV RNA (log scale)
- HIV Antibody
- Plasma RNA

CD4 levels initially increase, peak, and then decline. Plasma HIV RNA shows a similar trend but is on a log scale. HIV Antibody and Plasma RNA levels rise as CD4 levels decline, indicating progression of the infection. Medical Events are indicated by arrows and points on the graph.
Time to NP Impairment Split by CD4 Group

Proportion Unimpaired vs Time (years)

- CD4 ≥ 400
  - N = 58

- CD4 < 400
  - N = 16
Time to NP Impairment Split by Plasma HIV-RNA Group

Proportion Unimpaired

Time (years)

Plasma \leq 4.5
N = 52

Plasma > 4.5
N = 22
Time to NP Impairment Split by Highest Risk (Hi Plasma HIV-RNA/Low CD4) vs. All Other Risk Group Combinations

Plasma ≤ 4.5 logs vs. > 4.5 logs  CD4 ≥ 400 vs. < 400
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (n)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.4</td>
<td>10.3</td>
</tr>
<tr>
<td>Education</td>
<td>13.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Gender (%M)</td>
<td>78.6% (55)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62.9% (44)</td>
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</tr>
<tr>
<td>Black</td>
<td>22.9% (16)</td>
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</tr>
<tr>
<td>Hispanic</td>
<td>14.2% (10)</td>
<td></td>
</tr>
<tr>
<td>% Acute</td>
<td>24.3% (17)</td>
<td></td>
</tr>
<tr>
<td>Estimated duration of infection (months)</td>
<td>6.2</td>
<td>3.6</td>
</tr>
<tr>
<td>% Impaired</td>
<td>28.6% (20)</td>
<td></td>
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</tbody>
</table>
NP Impairment in AEH Cohort at Baseline and 6-month follow-up
Cerebral Blood Flow Changes in Controls, AEH and Chronic HIV cases

Altered NAA in AEH and Chronic HIV

Frontal Cortical Gray Matter

Centrum Semiovale White Matter

Lentz et al., 2009
Model for CNS Complications in Acute and Early HIV Infection

↑ Peak HIV Replication → ↑ Dissemination of HIV → ↓ CD4+ Nadir

↑ Depletion of GALT → ↑ Bacterial Translocation

↑ HIV Seeding of the CNS → ↑ HIV Replication in the CNS → ↑ Neuroinflammation

↑ Systemic Inflammation → ↑ Blood-Brain Barrier Injury → ↑ Neuronal Injury

CNS Complications
- Neurocognitive Impairment via NP Testing
- Neuroanatomic/metabolite worsening via Imaging
Plasma lipopolysaccharide (LPS) and sCD14 monocyte activation marker related to HAND in AIDS patients with CD4 < 300

Summary of HAND and AEH

» Neurocognitive impairment is present within 6 mos of infection
» 10% decline over 6 mos
» Associated with plasma biomarkers of neuronal injury [eg tau] and inflammation/cell migration (uPAR)
» Evidence of neuronal injury also on MRS (lower NAA)
» Increased CBF in basal ganglia (perhaps indicates inflammatory change)
» High VL and low CD4 increase hazard of HAND in future
HAND and AEH: examples of questions

» Do early gut associated lymphocyte (GALT) depletion, and bacterial translocation, trigger systemic inflammation favoring migration of HIV and immune cells into the CNS?

» Is GALT injury associated with spikes in VL that increase trafficking of HIV into CNS?

» Do drugs of abuse that modify immune responses, eg., methamphetamine; opioids amplify the above?

» Do coinfections, eg., TB, malaria, HCV also amplify these?

» Does acute treatment with CNS penetrating ARV abort these early CNS events?

» Utility of “neuroprotective” and “anti-inflammatory” adjuncts
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Thank you!

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Elevated Blood (but not CSF) Biomarkers associated with NP Impairment in AEH Cases

- Tau (plasma)
- uPAR (plasma)
- MCP-1 (CSF)