HIV associated CNS disease in the era of HAART

CSF/CNS penetration and efficacy
Acknowledgements

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HAND
HIV-associated neurocognitive disorders

• HAND is umbrella definition comprising:
  – ANI: asymptomatic neurocognitive impairment
  – MND: mild neurocognitive disorder
  – HAD: HIV-associated dementia

Antinori, Neurology 2007
History

- 1986: AIDS dementia complex:
  - Cognition
  - Behavior
  - Motor function

- 1989: zidovudine: declining incidence; virtual disappearance with HAART
• Complaints of:
  – Memory problems
  – Slowness
  – Difficulties in:
    • concentration
    • planning
    • multitasking
Recent cohort studies

• 15-60% cognitive impairment
Neuropathology

- Leuko-encephalopathy
- HIV-encephalitis
- Microglial cells, perivascular macrophages, multinucleated giant cells
- Infected astrocytes
Clinical approach of cognitive impairment

• Rule out depression

• Neuropsychological assessment

• MRI

• CSF
Cognitive domains

- Speed of information processing
- Attention/working memory
- Executive functioning
- Memory
- Verbal/language
- Sensory-perceptual
- Motor skills
Mini-mental state examination (MMSE) 
Folstein test (1975)

• 30-point questionnaire test used to screen for cognitive impairment (and to follow course of cognitive changes over time)
• In about 10 minutes samples various functions, including arithmetic, memory and orientation
## Mini-mental state examination (MMSE)  
Folstein test (1975)

<table>
<thead>
<tr>
<th>Category</th>
<th>Possible points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation to time</td>
<td>5</td>
</tr>
<tr>
<td>Orientation to place</td>
<td>5</td>
</tr>
<tr>
<td>Registration</td>
<td>3</td>
</tr>
<tr>
<td>Attention and calculation</td>
<td>5</td>
</tr>
<tr>
<td>Recall</td>
<td>3</td>
</tr>
<tr>
<td>Language</td>
<td>2</td>
</tr>
<tr>
<td>Repetition</td>
<td>1</td>
</tr>
<tr>
<td>Complex commands</td>
<td>6</td>
</tr>
</tbody>
</table>
Mini-mental state examination (MMSE)
Folstein test (1975)

- Score of ≥ 25 (out of 30) effectively normal (intact)
- 21-24: mild cognitive impairment
- 10-20: moderate
- ≤ 9: severe
HIV dementia Scale

- Memory - registration
- Attention
- Psychomotor speed
- Memory-Recall
- Construction

- Maximum Score: 16
- Score ≤ 10: HAD
CSF markers of HIV CNS infection

• Virological Markers
  – e.g.: HIV-1 RNA, viral sequences

• Host Response Markers
  – e.g.: beta₂ microglobulin, neoterin

• Markers of CNS Damage
  – e.g.: Tau protein
What is going on?

- Do we see more cognitive problems?
- Is it more than normal aging?
- Every infected person? Subgroups?
- What kind of problems do we see? HAD?
- Diagnostic approach?
- What is the course?
- Is it HIV? Is it HAART? Is it aging + HIV?
- Do we need to change treatment?
Neuro-pathogenesis

- Ongoing HIV-replication
- Persistent immune activation/neuroinflammation
- Vascular abnormalities
- Premature aging
- Toxicity of HAART
HIV-Associated Neurocognitive Disease

- Risk factors?
- Mechanisms?

HIV-associated neurocognitive disease (HAND)

HAART reduces the occurrence of worst effects ...

... but improved survival has meant an increase in overall prevalence

Do CSF concentrations reflect brain concentrations?

CNS penetration of antiretroviral drugs

How strongly is it linked to cognitive improvement?

How strongly is it linked to reduced neurological damage?

How strongly is it linked to cognitive improvement?

How meaningful are current penetration scores?
How important is CNS penetration?

- CNS penetrating drugs are associated with reductions in cerebrospinal fluid (CSF) viral load\(^1\)
- Viral suppression in the CSF is thought to be associated with neurocognitive improvement\(^1\)
- ARV treatment regimens that can control CSF HIV replication may help to prevent HAND\(^2\)
- However, conflicting data exist;\(^3\) for example, in a recent study white matter injury was not related to either viral load or CNS penetration of ARVs\(^4\)

Cerebrospinal fluid is a distinct virologic compartment for HIV-1

- Paired CSF and plasma samples collected from HIV-infected patients with neurologic signs/symptoms or with systemic non-Hodgkin’s lymphoma
  - ART concentrations in CSF varied but were always lower than in plasma
  - Many common antiretroviral agents were undetectable in CSF
  - Fold changes in susceptibility for $\geq 1$ drug differed between CSF and plasma in 18 of 40 patients (45%)
- In early HIV disease, CSF and peripheral virus are similar
- In later HIV disease, CSF virus is phylogenetically distinct from virus in the periphery

<table>
<thead>
<tr>
<th>CNS penetration-effectiveness (CPE) rank</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemical properties</strong></td>
<td>Suggestive of poor penetration</td>
<td>Do not clearly support penetration</td>
<td>Support high penetration</td>
</tr>
<tr>
<td><strong>CSF concentration</strong></td>
<td>Below quantifiable level or &lt; wild-type IC$_{50}$</td>
<td>Not consistently detectable. Measureable concentrations not consistently exceeding wild-type IC$_{50}$</td>
<td>Measurable and consistently exceeds wild-type IC$_{50}$</td>
</tr>
<tr>
<td><strong>Alterations in viral load (VL) or cognition</strong></td>
<td>No reduction in CSF VL and no improvements in cognition</td>
<td>—</td>
<td>Reduction in CSF RNA or improved cognition</td>
</tr>
</tbody>
</table>


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CNS penetration-effectiveness rank for treatment regimens

- Individual ARV drugs are assigned a penetration rank of
  - 0 (low)
  - 0.5 (intermediate)
  - 1 (high)
- The CPE rank for a treatment regimen is the sum of the individual penetration ranks
Regimen CPE rank and detectable CSF VL

Patients with lower CNS penetration-effectiveness rank are more likely to have detectable CSF VL
Figure to be redrawn
Niall Harrison; 24-9-2009
CNS penetration effectiveness (CPE)

Subjects with lower CNS Penetration-Effectiveness (CPE) scores were more likely to have detectable CSF viral load

Letendre S et al. (CHARTER Group) Arch Neurol. 2008;65(1):65-70

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## Antiretroviral Treatment

**CNS Penetration-Effectiveness Scores**

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>Abacavir</th>
<th>Emtricitabine</th>
<th>Didanosine</th>
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<tr>
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Antiretroviral Treatment

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# Antiretroviral Treatment

**CNS Penetration-Effectiveness Scores**

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Efavirenz CSF concentrations exceed the wild-type IC$_{50}$ and may inhibit HIV replication in the CNS

Emtricitabine CSF concentrations

Emtricitabine CSF concentration are above the wild-type IC₅₀ in most individuals and may be sufficient to inhibit HIV replication in the CNS

1. Best B, *et al.* 16th CROI, Montreal 2009, #702:


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Abacavir Concentration (ng/mL)

Time After Dose (hours)

CSF penetration was 36% of plasma concentrations suggesting that ABC penetration may be sufficient to reduce viral replication in the CNS.

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Tenofovir CSF concentrations

CSF penetration was 4% of plasma concentrations and did not exceed the wild-type IC$_{50}$ of tenofovir, so may not provide enough CNS protection

ATZ/(r) CSF concentrations 100-fold lower than plasma

Atazanavir may not protect against HIV replication in the CSF

Best BM et al. AIDS 2009, 23:83–87

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In patients with typical plasma levels of LPV concentrations exceed those needed to inhibit HIV replication in spite of > 98% plasma protein binding, LPV penetrates into the CNS and may control viral load.
<table>
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<th>4</th>
<th>3</th>
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<td>Darunavir-r</td>
<td>Atazanavir</td>
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<td></td>
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<td></td>
<td>Fosamprenavir-r</td>
<td>Atazanavir-r</td>
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<tr>
<td>Entry/Fusion Inhibitors</td>
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<td>Maraviroc</td>
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<td>Enfuvirtide</td>
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<tr>
<td>Integrase Inhibitors</td>
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<td>Raltegravir</td>
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- N = 2636; on ART ≥ 6 weeks; pVL < 50 c/mL

- NPZ3 scores associated with higher CPE among participants taking more than three antiretrovirals, but not among those taking three or less drugs

- Use of antiretroviral drugs with better estimated CNS penetration may be associated with better neurocognitive functioning; some people may require more than three drugs to treat HIV in the CNS
Cornelissen M et al.
Antiviral Therapy: in press.

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Adjunctive treatments

Psychostimulants, selegiline, valproic acid, lexipafant, calcium channel blocker, memantine, minocycline, lithium, antioxidants, serotonin reuptake inhibitor nanoparticles

do not work.
Discussion Questions

• In your experience, how prevalent is cognitive dysfunction (HAND) remain in clinical practice?
  – How common is HAND in patients with viral suppression?
  – Are specific regimens more associated than others with improvements or worsening of cognitive dysfunction?

• Is the CPE scoring system a useful tool in clinical practice?

• What studies need to be done to assess the effect of specific ARV regimens on HAND?

• Will CNS (or semen) penetration be an important consideration in regimen choice / drug development in the future?