Prevention of Neurocognitive impairment

Paola Cinque
San Raffaele Scientific Institute
Milano, Italy

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Potential causes/risk factors of cognitive decline in persons living with HIV

1. Direct HIV damage in CNS (HIV-associated NCI)
2. Previously established irreversible tissue damage by HIV or other causes (legacy effect)
3. Aging
4. Psychiatric disorders
5. Drugs, alcohol abuse
6. Metabolic problems
7. Cerebro-vascular disease
8. Alzheimer’s and other neurodegenerative diseases
9. Drug toxicity (ART, other drugs) ?
Potential causes/risk factors of cognitive decline in persons living with HIV

<table>
<thead>
<tr>
<th>Number</th>
<th>Cause</th>
<th>Preventability</th>
</tr>
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<tbody>
<tr>
<td>1.</td>
<td>Direct HIV damage in CNS (HIV-associated NCI)</td>
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</tr>
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</tr>
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</tr>
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<td>6.</td>
<td>Psychiatric disorders</td>
<td>PREVENTABLE</td>
</tr>
<tr>
<td>7.</td>
<td>Alzheimer's and other neurodegenerative diseases</td>
<td>NON PREVENTABLE</td>
</tr>
<tr>
<td>8.</td>
<td>Previously established irreversible tissue damage by HIV or other causes (legacy effect)</td>
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</tr>
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<td>9.</td>
<td>Aging</td>
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Potential causes/risk factors of cognitive decline in persons living with HIV

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Prevention of HIV replication and damage in CNS (HIV-associated NCI)

All cART regimens control HIV-associated NCI by suppressing HIV replication in the CNS (consequently to VL control in blood)

vs.

‘Neuro-active’ ART (with enhanced CNS penetration/efficacy) is needed to suppress HIV replication in the CNS
### NCI and ART neuropenetration

<table>
<thead>
<tr>
<th>Study</th>
<th>Cysique</th>
<th>Tozzi</th>
<th>Smurzynski</th>
<th>Marra</th>
<th>Winston</th>
<th>Arendt</th>
<th>Garvey</th>
<th>Rourke</th>
<th>Ciccarelli</th>
<th>Robertson</th>
<th>Kahouadji</th>
<th>Ellis</th>
</tr>
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<tbody>
<tr>
<td>UCSD CIT</td>
<td>INMI</td>
<td>ALLRT</td>
<td>ACTG 736</td>
<td>ALTAIR</td>
<td>Dusseldorf NA Cohort</td>
<td>Imperial College, UK</td>
<td>OHTN Cohort Study</td>
<td>UCSC</td>
<td>ACTG 5199</td>
<td>INSERM</td>
<td>HNRP/UCSD</td>
<td></td>
</tr>
<tr>
<td>Sample Size</td>
<td>37</td>
<td>185</td>
<td>2,636</td>
<td>26</td>
<td>30</td>
<td>3,883</td>
<td>101</td>
<td>545</td>
<td>101</td>
<td>860</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td>CPE: CSF VL</td>
<td>Lower VL</td>
<td>No CSF</td>
<td>No CSF</td>
<td>Lower VL</td>
<td>No CSF</td>
<td>Lower VL</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No CSF</td>
<td>No effect</td>
</tr>
<tr>
<td>Number of NP Tests</td>
<td>6</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>CogState</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>18</td>
<td>6</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>CPE: NP Tests</td>
<td>Better</td>
<td>Better</td>
<td>Better (only by &gt;3 drugs)</td>
<td>Poorer</td>
<td>Poorer</td>
<td>Better</td>
<td>No effects</td>
<td>Not conclusive</td>
<td>Better</td>
<td>No effect</td>
<td>Poorer</td>
<td>No effect</td>
</tr>
<tr>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Controlled</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Norms for NP Change</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
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</table>


(Courtesy of S. Letendre, 2016)
Randomized Clinical Trial of Antiretroviral Therapy for Prevention of HAND in naïve pts (Beijing, China)

NVP+AZT+3TC vs. EFV+TDF+3TC

- 1036 pts, no NCI
- 97-100% M, median CD4 235-222/µL, median logVL 4.2 c/mL
- 8 test battery

Scott Letendre et al., CROI 20
CSF viral escape

- On ART > 6/9 months
- CSF VL > LLD (if plasma VL suppressed) or CSF VL > plasma VL (if plasma VL >50)
- Symptomatic or asymptomatic

Neuro-symptomatic CSF viral escape (meningoencephalitis)

- M, 26
- **2010**: Headache, disarthria, ataxia (days)

- History of systemic OIs
- CD4 nadir: 9
- 2009: Starts ART (AZT, 3TC, LPV/r)
- Change to **TDF, FTC, ATV**

- CD4 290
- **Plasma HIV 98 c/mL**
- CSF HIV 5200 c/mL
- CSF cells: 200/µL

No CSF mutations to NRTIs and PIs

*Peluso M et al. AIDS 2012*
Neuro-symptomatic CSF viral escape (meningoencephalitis)

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No CSF mutations to NRTIs and PIs

→ Resolution by cART optimization for neuropenetration (AZT, 3TC, DRV/r bid)
CD4 cells and VL values in patients with neuro-symptomatic CSF escape

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood CD4 (cells/µL)</td>
<td>520 (308–592)</td>
<td>107–660</td>
</tr>
<tr>
<td>Nadir blood CD4 (cells/µL)</td>
<td>55 (12–145)</td>
<td>2–250</td>
</tr>
<tr>
<td>CSF WBC (cells/µL)</td>
<td>22 (10–55)</td>
<td>0–200</td>
</tr>
<tr>
<td>Plasma HIV (log$_{10}$ copies/mL)</td>
<td>1.69 (1.69–2.68)</td>
<td>1.69–2.68</td>
</tr>
<tr>
<td>CSF HIV (log$_{10}$ copies/mL)</td>
<td>3.01 (2.76–3.72)</td>
<td>2.13–4.11</td>
</tr>
<tr>
<td>CSF:plasma difference (log$_{10}$ copies/mL)</td>
<td>1.25 (1.06–1.44)</td>
<td>0.44–2.23</td>
</tr>
</tbody>
</table>

Possible risk factors for symptomatic CSF escape

• Presence and size of brain ‘reservoir’ (low nadir CD4 cells, previous HIV-E, previous CSF-escape)

• ARV drug resistance
• Inadequate ART adherence
• Inadequate efficacy of individual drugs/regimens
  • CNS ‘penetration’
  • Efficacy in macrophages/microglial cells
Prevention of CSF escape

• Presence and size of brain ‘reservoir’ (low nadir CD4 cells, previous HIV-E, previous CSF-escape)

• ARV drug resistance
• Inadequate ART adherence
• Inadequate efficacy of individual drugs/regimens
  • CNS ‘penetration’
  • Efficacy in macrophages/microglial cells

In persons at risk:
→ Clinical monitoring for CSF escape
→ ART with enhanced CNS penetration/efficacy?
Cerebral small vessel disease (CSVD) in HIV-infected cART-controlled patients

ANRS EP51 MICROBREAK (NCT02082574) cross-sectional study (June 2013 - May 2016)

- CSVD prevalence by MRI in treated HIV, >50 years with controlled VL for >12 months vs. HIV negative controls

- 456 HIV+ and 154 HIV-neg

- CSVD prevalence:
  → HIV-pos: 51.5%
  → HIV-neg: 36.4%
  OR 2.3 (95% CI: 1.5–3.6)

- Independent predictors of risk in HIV+:
  - Older age
  - Hypertension
  - Lower CD4 nadir

Mouligner A et al., Clinical Infectious Diseases® 2018;66(11):1762–9
Cardiovascular and cerebrovascular disease: Potential mechanisms of heightened atherogenesis in HIV
Association of Macrophage Inflammation Biomarkers with Progression of Subclinical Carotid Artery atherosclerosis in HIV-infected patients

Hanna DB et al., The Journal of Infectious Diseases 2017;215:1352-
Epidemiology of cerebrovascular disease in a post-cART era

Data from the Nationwide Inpatient Sample from 1995 to 2010.

Patients with ischemic stroke and AIDS identified using ICD-9 codes.

1,874,067 hospitalizations for ischemic stroke over 16 years
Greater Risk of Stroke of Undetermined Etiology in a Contemporary HIV Cohort Compared to non-HIV

Stroke risk factors that are not within your control

- Age
- Sex
- Race
- Family history
- Prior stroke, TIA or heart attack

Understanding stroke risk, American Hearth Association
http://www.strokeassociation.org/STROKEORG/AboutStroke/UnderstandingRisk/Understanding-Stroke-Risk_UCM_308539_SubHomePage.jsp
Stroke risk factors that you can control, treat and improve

- High blood pressure
- Smoke
- Diabetes
- Diet
- Physical activity
- Obesity
- High blood cholesterol
- Carotid artery disease
- Peripheral artery disease
- Atrial fibrillation
- Other heart disease
- Sickle cell disease

Understanding stroke risk, American Heart Association
http://www.strokeassociation.org/STROKEORG/AboutStroke/UnderstandingRisk/Understanding-Stroke-Risk_UCM_308539_SubHomePage.jsp
Additional factors that may be linked to higher stroke risk

- Geographic location
- Socio-economic factors
- Alcohol abuse
- Drug abuse
- Sleep habits
Conclusions

Prevention is an important component towards control of neurocognitive impairment in HIV-infected persons.