HIV, HCV, Drug Abuse and the Brain

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Range of HIV Associated Neurocognitive Disorders (HAND)

- Asymptomatic Neuropsychological Impairment: abnormality in two or more cognitive abilities
- Mild Neurocognitive Disorder: cognitive impairment with mild functional impairment
- HIV-associated Dementia: marked cognitive impairment with marked functional impairment
Although Combination Antivirals Improve Health and Prolong Survival, NeuroAIDS Remains Prevalent.
Prevalence of HAND by Stage of HIV Disease

- HIV- (n=212): 15.1%
- CDC-A (n=437): 26.5%
- CDC-B (n=213): 25.4%
- CDC-C (n=113): 17.7%
Proportions of Persons Judged to have Global NP Impairment that have Specific Ability Deficit

PERCENT IMPAIRED

<table>
<thead>
<tr>
<th>Ability</th>
<th>Percent Impaired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>61</td>
</tr>
<tr>
<td>Learning</td>
<td>57</td>
</tr>
<tr>
<td>Verbal</td>
<td>44</td>
</tr>
<tr>
<td>Motor</td>
<td>41</td>
</tr>
<tr>
<td>Memory</td>
<td>38</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>32</td>
</tr>
<tr>
<td>Sensory</td>
<td>28</td>
</tr>
<tr>
<td>Abstraction</td>
<td>24</td>
</tr>
</tbody>
</table>
### NP Course for HIV Neurocognitive States (from HNRC, N=534)

<table>
<thead>
<tr>
<th>State</th>
<th>Count</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>stably normal</td>
<td>249</td>
<td>47%</td>
</tr>
<tr>
<td>stably impaired</td>
<td>60</td>
<td>11%</td>
</tr>
<tr>
<td>stably improved</td>
<td>95</td>
<td>18%</td>
</tr>
<tr>
<td>stably declined</td>
<td>24</td>
<td>4%</td>
</tr>
<tr>
<td>fluctuated</td>
<td>102</td>
<td>19%</td>
</tr>
</tbody>
</table>

Dynamic Nature of White Matter Change

Increasing WM Abnormalities

Baseline

One year

Two years
Dynamic Nature of White Matter Change

Decreasing WM Abnormalities

Baseline

One year

Two years
Meaning of NP Impairment: Employment

- NP Normal (n=152): 7.9%
- NP Impaired (n=80): 17.5%

Meaning of NP Impairment:

- Employment
Mean Number of Accidents on City Driving Simulation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of Accidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP Normal</td>
<td>1.5</td>
</tr>
<tr>
<td>NP Impaired</td>
<td>2.1</td>
</tr>
<tr>
<td>MND</td>
<td>3.2</td>
</tr>
</tbody>
</table>
Adherence to Antiretrovirals Related to Neurocognitive Impairment

Percent That Followed Schedule “Most of the Time”

Percent That Followed Specific Instructions Regarding Medications “Most of the Time”
Longitudinal Course of Participants who were Neurocognitively Normal at Baseline

Neurocognitively Normal (N=130)

Normal 88%
- Alive 77%
- Deceased 23%

Fluctuating 12%
- Alive 50%
- Deceased 50%

Participants with annual and/or semiannual assessments over a minimum of 2 and up to 8 years
Possible Mechanisms of Neurotoxicity in HIV-1 Infection

Macrophage

Astrocyte

Cytokines (e.g., TNFa, IL-6)

HIV

QA

GP120

Neuron

Cytokines

Protective Factors

VIP Receptor

NMDA Receptor

Chemokine Receptor

Ca++

VIP

GAL

GP120

Macrophage

HIV
Synaptophysin and MAP-2 Immunostaining
Dendritic Complexity Relates to the Severity of HAND

Neurocognitive Rating
Percent Area Occupied by Dendrites

rho = -.67; p < .001

rho = -0.67; p < 0.001
Increased Abnormal White Matter Is Related to Dendritic Loss at Autopsy
Cofactors in HIV Associated Neurocognitive Complications

- Drug Abuse - example of methamphetamine
- Coinfection with Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments
Percent Having Global NP Impairment by Methamphetamine Abuse and HIV Status

- HIV-: ~10%
- HIV+: ~70%
- HIV-: ~30%
- HIV+: ~70%
Significant Regional Volume Alterations Related to METH and/or HIV

- METH (increases)
- HIV (decreases)
- METH & HIV (opposing effects)
Association of Cortical Volumes with Impairment

For HIV+:
- Global Impairment Rating vs. Cortex Volume
- Correlation coefficient: $r = -0.41$, $p < 0.05$

For METH+:
- Global Impairment Rating vs. Cortex Volume
- Correlation coefficient: $r = 0.46$, $p < 0.05$
Association of Cortical Volumes with Attention Deficits

**HIV+**

- \( \beta = -0.43, p = 0.003 \)

**METH+**

- \( \beta = 0.26, p = 0.025 \)
MAP-2 in Midfrontal Cortex of HIV+ Cases With or Without HIVE and With or Without METH

A) Preserved neuronal and dendritic structure in HIV patient HIVE (-) METH (-).
B) Moderate neuronal and dendritic damage in a HIVE (-) METH (+) patient.
C) Moderate to severe neuronal damage in an HIVE (+) METH (-) patient.
D) Severe neuronal and dendritic damage in an HIVE (+) METH (+) patient.
Bar = 25 microns
Degeneration of Interneurons in HIVE+ METH+ Users

<table>
<thead>
<tr>
<th></th>
<th>HIV- METH-</th>
<th>HIV+ METH-</th>
<th>HIV+ METH+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calbindin</td>
<td>No Alterations</td>
<td>Neuronal Damage</td>
<td>Severe Neuron Loss</td>
</tr>
<tr>
<td>Parvalbumin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Loss of Calbindin Interneurons Is Associated With Cognitive Impairment and Memory Loss in METH Users With HIVE

HIV+ (Control)

HIVE+ METH-

HIVE+ METH+

Calbindin Immunoreactive Interneurons

Cell density per 10^4 cubic mm

HIV+ Control  HIVE+ METH-  HIVE+ METH+

Calbindin Interneurons (per 0.1 mm^2)

r = -0.5, n=20, p<0.05

Heaton Global Score

Calbindin interneurons (x 0.1 mm^2)

r = -0.695, n=20, p<0.01.

Memory Score

Methamphetamine (METH) use is associated with a loss of calbindin immunoreactive interneurons in the brains of individuals with HIV (HIV+). This loss is correlated with cognitive impairment and memory loss, as indicated by lower scores on the Heaton Global Score and Memory Score.
Cofactors in HIV Associated Neurocognitive Complications

- Drug Abuse - example of methamphetamine
- Coinfections - example of Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments
Rate of Neurocognitive Impairment in HCV+ Persons in Anhui, China

**Graph:**
- X-axis: HCV- (n = 147) vs. HCV+ (n = 51)
- Y-axis: Percent NP Impaired
- **HCV-:** 5%
- **HCV+:** **28%**
- **Statistical Significance:** ***p < .001**
Panel A shows worse neurocognitive score in HCV+ vs HCV-
Panel B shows as the number of comorbid conditions increases, neurocognitive performance worsens. The risks, in various combinations include HIV, HCV, and methamphetamine dependence
Cellular Localization of HCV in NNTC Brains

Letendre et al 2007 JID 196, 361-370

Polyclonal antibody to HCV NS5A structural protein

Monoclonal antibody to NS5A

Monoclonal antibody to HCV core antigen

Astrocytic localization

Macrophage localization

Letendre et al 2007 JID 196, 361-370
Neurobehavioral Effects of HIV infection in China
Robert Heaton, Ph.D. and Colleagues

• UCSD
  – L. Cysique
  – J. Hampton Atkinson
  – Donald Franklin
  – Igor Grant
  – Hua Jin
  – Deborah Lazzaretto
  – Scott Letendre
  – Thomas Marcotte
  – Ofilio Vigil

• China
  – Zunyou Wu ¹
  – Xin Yu ²
  – Chuan Shi ²
  – Yun Gao ¹
  – Ning Dong ¹
  – Yihua Fan ²

¹ China CDC, NCAIDS
² Peking University, Institute of Mental Health
HIV/AIDS Cases by Geographic Region and Proposed Data Collection Sites in China

- Beijing
- Anhui
- Yunnan

Legend:
- 1-100
- 101-500
- 501-1000
- 1001-5000
- 5001-10000
- >10000
Anhui Cohort

• 400 participants were enrolled
• 198 HIV- and 202 HIV+
• Primary risk factor for HIV was blood product donations (former plasma donors)
Overview of Methods

- Neuropsychological battery: 15 tests covering 7 ability domains
- Standardized medical/neurological history and examination
- Psychiatry: structured assessments of substance use disorders and affective disorders
Demographic Characteristics of Anhui Cohort: All Former Plasma Donors

<table>
<thead>
<tr>
<th></th>
<th>HIV- (n = 198)</th>
<th>HIV+ (n = 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>40.3 ± 6.3</td>
<td>40.2 ± 6.4</td>
</tr>
<tr>
<td>Education</td>
<td>5.8 ± 2.1</td>
<td>5.5 ± 2.3</td>
</tr>
<tr>
<td>Male</td>
<td>60.6%</td>
<td>60.9%</td>
</tr>
<tr>
<td>Lifetime plasma donations</td>
<td>13.2 ± 23.8</td>
<td>52.3 ± 95.6</td>
</tr>
</tbody>
</table>

***p<.0001
## Demographic Characteristics (2)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV-</th>
<th>HIV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speaks Fuyang dialect</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Speaks Mandarin</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>Han Ethnicity</td>
<td>99.5%</td>
<td>99.5%</td>
</tr>
<tr>
<td>Grew up in rural area</td>
<td>100%</td>
<td>99%</td>
</tr>
<tr>
<td>Resides in rural area</td>
<td>100%</td>
<td>99.5%</td>
</tr>
<tr>
<td># family members in home</td>
<td>5.2 ± 1.2</td>
<td>5.1 ± 1.4</td>
</tr>
<tr>
<td>Married*</td>
<td>95.5%</td>
<td>88.6%</td>
</tr>
<tr>
<td>Widowed*</td>
<td>4.5%</td>
<td>10.9%</td>
</tr>
</tbody>
</table>

*p < .05
## HIV Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV+ Anhui</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 202</td>
</tr>
<tr>
<td>% AIDS</td>
<td>56.4%</td>
</tr>
<tr>
<td>Current CD4</td>
<td>350 ± 194</td>
</tr>
<tr>
<td>nadir CD4</td>
<td>252 ± 157</td>
</tr>
<tr>
<td>Log$_{10}$ HIV RNA plasma*</td>
<td>4.2 (IQR = 3.5-4.7) [Min- Max 2.1-5.5]</td>
</tr>
</tbody>
</table>

* NucliSens EasyQ HIV-1 from bioMérieux
  EasyQ assay uses real-time NASBA amplification and molecular beacon detection technology and has a range of 50 to 3 million IU(copies)/mL.
**CDC Stages in HIV+**

<table>
<thead>
<tr>
<th>CDC Stage</th>
<th>N</th>
<th>Percent</th>
<th>Current CD4</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>15</td>
<td>7.4</td>
<td></td>
<td>637</td>
</tr>
<tr>
<td>A2</td>
<td>52</td>
<td>26</td>
<td></td>
<td>393</td>
</tr>
<tr>
<td>A3</td>
<td>44</td>
<td>22</td>
<td></td>
<td>292</td>
</tr>
<tr>
<td>B1</td>
<td>1</td>
<td>0.5</td>
<td></td>
<td>610</td>
</tr>
<tr>
<td>B2</td>
<td>20</td>
<td>10</td>
<td></td>
<td>372</td>
</tr>
<tr>
<td>B3</td>
<td>40</td>
<td>20</td>
<td></td>
<td>271</td>
</tr>
<tr>
<td>C2</td>
<td>7</td>
<td>3.5</td>
<td></td>
<td>609</td>
</tr>
<tr>
<td>C3</td>
<td>23</td>
<td>11</td>
<td></td>
<td>199</td>
</tr>
</tbody>
</table>
## HIV Treatment Regimens

<table>
<thead>
<tr>
<th>HIV+ on ART (N = 115) *</th>
<th>HIV+ N = 202</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent on HAART **</td>
<td>88%</td>
</tr>
<tr>
<td>Percent on Dual-therapy</td>
<td>9%</td>
</tr>
<tr>
<td>Percent Monotherapy</td>
<td>3%</td>
</tr>
<tr>
<td>Treatment duration (months)</td>
<td>15 ± 9</td>
</tr>
<tr>
<td>Reported “adherence always”</td>
<td>98.3%</td>
</tr>
<tr>
<td>Chinese traditional medicine</td>
<td>2.5%</td>
</tr>
</tbody>
</table>

*On ART for AIDS = 77%; Non-AIDS = 31%

** HAART = composed of at least 3 ART
Proportion of NP Impairment among HIV-, HIV+ and AIDS Participants

NP Impairment was defined as GDS $\geq 0.5$

<table>
<thead>
<tr>
<th>Category</th>
<th>% NP-impairment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>HIV+ non-AIDS</td>
<td>24%</td>
<td>0.07</td>
</tr>
<tr>
<td>AIDS</td>
<td>37%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

N = 198
N = 88
N = 114

NP Impairment was defined as GDS $\geq 0.5$
<table>
<thead>
<tr>
<th></th>
<th>NP Impaired HIV+ (n = 63)</th>
<th>NP Normal HIV+ (n = 139)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current CD4 below 200</td>
<td>34%</td>
<td>22.5%</td>
</tr>
<tr>
<td>Nadir CD4 below 200</td>
<td>64%</td>
<td>46% *</td>
</tr>
<tr>
<td>Currently on ART</td>
<td>75%</td>
<td>49% **</td>
</tr>
</tbody>
</table>

No correlation between NP impairment (GDS) and Log\(_{10}\) HIV RNA, or Log\(_{10}\) Beta-2 microglobulin

* * p < .05  ** * p < .001
HIV Status, NP Impairment and Unemployment

- HIV effect: $p < .0001$
- NP Impairment: effect $p = .40$
- Interaction: $p = .24$
Prevalence of HCV Infection Among Anhui Participants

HIV- (n = 198)
- 74% HCV-
- 26% HCV+

HIV+ (n = 202)
- 54% HCV-
- 46% HCV+
Individual and Combined Effects of HIV and HCV on NP Status

**Percent NP Impaired**

- HIV- HCV- (n = 147)
- HIV+ only (n = 110)
- HCV+ only (n = 51)
- HIV+ HCV+ (n = 92)

*** p < .001
Proportion of NP Impairment Among HIV-, HIV+ and AIDS Participants

*(HCV- Only)*

**Proportions:**
- HIV-: 8.8% (N = 147), *P* = .02
- HIV+ non-AIDS: 24% (N = 38), *P* = .29
- AIDS: 33% (N = 72), *P* < .0001
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The San Diego HIV Neurobehavioral Research Center (HNRC) Group is affiliated with
the University of California, San Diego, the Naval Hospital, San Diego, and
the Veterans Affairs San Diego Healthcare System,

and includes:

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**Neurobehavioral Component:** Robert K. Heaton, Ph.D. (P.I.), Mariana Cherner, Ph.D., Steven Paul Woods, Psy.D., David
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Clinical Trials Component: J. Allen McCutchan, M.D., J. Hampton Atkinson, M.D., Ronald J. Ellis, M.D., Ph.D., Scott Letendre, M.D.;

Participant Accrual and Retention Unit: J. Hampton Atkinson, M.D. (P.I.), Rodney von Jaeger, M.P.H.;

Data Management Unit: Anthony C. Gamst, Ph.D. (P.I.), Clint Cushman (Data Systems Manager), Daniel R. Masys, M.D. (Senior Consultant);

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HIV, HCV, Drug Abuse and the Brain

Thank You for Your Attention!

Igor Grant M.D.

HIV Neurobehavioral Research Center,
University of California, San Diego