MULTIFACETED INFLUENCES ON NEUROAIDS: EFFECTS OF METHAMPHETAMINE, HCV AND AGE

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Range of HIV Associated Neurocognitive Disorders (HAND)

- HIV associated Dementia
  - marked cognitive impairment with marked functional impairment

- Mild Neurocognitive Disorder
  - cognitive impairment with mild functional impairment

- Asymptomatic Neuropsychological Impairment
  - abnormality in two or more cognitive abilities

- Neuropsychological Deficit
  - clear abnormality in one cognitive ability

Range of HIV Associated Neurocognitive Disorders (HAND)
Updated research nosology for HIV-associated neurocognitive disorders
A. Antinori, G. Arendt, J. T. Becker, B. J. Brew, D. A. Byrd, M. Cherner, D. B.
R. Robertson, N. Sacktor, V. Valcour and V. E. Wojna
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This information is current as of October 29, 2007

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
http://www.neurology.org/cgi/content/full/69/18/1789
Prevalence of HAND by Stage of HIV Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>CDC A (n=437)</th>
<th>CDC B (n=213)</th>
<th>CDC C (n=113)</th>
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<tbody>
<tr>
<td>HIV-</td>
<td>15.1%</td>
<td>26.5%</td>
<td>25.4%</td>
</tr>
<tr>
<td>CDC A</td>
<td>0.5%</td>
<td>28.3%</td>
<td>17.7%</td>
</tr>
<tr>
<td>CDC B</td>
<td>4.8%</td>
<td>18.3%</td>
<td>1.8%</td>
</tr>
<tr>
<td>CDC C</td>
<td>1.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% with Disorder

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Although combination antivirals improve health and prolong survival, NeuroAIDS remains prevalent.
NP Course for HIV neurocognitive states N=534

Definitional Criteria Work Group 1: Toward an updated nosology for HIV-associated neurocognitive disorders
Meaning of NP Impairment: Employment

<table>
<thead>
<tr>
<th>% Unemployed</th>
<th>Normal (N=152)</th>
<th>Impaired (N=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.9%</td>
<td>17.5%</td>
<td></td>
</tr>
</tbody>
</table>

p < 0.05
Mean Number of Accidents on City Driving Simulation

- NP Normal: 1.5
- NP Impaired: 2.1
- MCMD: 3.2
Adherence to Antiretrovirals Related to Neurocognitive Impairment

% That Followed Schedule “Most of the Time”

NP Unimpaired (N=19) | NP Impaired (N=8)

% That Followed Specific Instructions Re Meds “Most of the Time”

NP Unimpaired (N=15) | NP Impaired (N=8)
Proportions of Persons Judged to have 
Global NP Impairment that have 
Specific Ability Deficit

<table>
<thead>
<tr>
<th>Ability</th>
<th>% Impaired</th>
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<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>
Synaptophysin & MAP-2 Immunostaining

HIV-  HIV+

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Dendritic Complexity in Subjects with Varying Levels of Cognitive Impairment
Relation of Dendritic Damage to Neurocognitive Impairment

rho = -.67; p < .001
Increased abnormal white matter is related to dendritic loss at autopsy.

- **HIV-**
- **HIV+**

![Graph showing the relationship between Abnormal White Matter Volume and MAP2 (% cortex occupied by dendrites).](image-url)
Cofactors in HIV Associated Neurocognitive Complications

- Drug Abuse - example of methamphetamine
- Coinfection with Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments
Scott et al 2007 Neuropsych Rev
Long Term Neurocognitive Effects Methamphetamine vs. Cannabis

Scott et al 2007 Neuropsych Rev; Grant et al 2003 JINS
MA and HIV

- ~60% of persons seeking MA tx are HIV infected (Peck et al., 2005)

- MA use associated with:
  - Loss of interneurons (Chana et al., 2007)
  - Additive NP effects (Rippeth et al., 2004)
    - Immunocompromise (Carey et al., 2006)
  - HIV drug resistance (Colfax et al., 2007)
  - Problems in everyday functioning (Sadek et al., in press)
    - Poor ARV adherence (Reback et al., 2003)
% Having Global NP Impairment by Methamphetamine Abuse and HIV Status

- HIV- Non-Meth Abusing Group
- HIV+ Meth Abusing Group
- HIV- Meth Abusing Group
- HIV+
Significant regional volume alterations related to METH and/or HIV

- METH (increases)
- HIV (decreases)
- METH & HIV (opposing effects)
Meth have larger Accumbens volume for age relative to controls
Association of Cortical Volumes with Impairment

HIV+:
- $r = -0.41, p < 0.05$

METH+:
- $r = 0.46, p < 0.05$
Association of Cortical Volumes with Attention Deficits

HIV+  

CEREBRAL CORTEX VOLUME

CLINICAL RATING OF ATTENTION

\[ \beta = -0.43, p = 0.003 \]

METH+

CEREBRAL CORTEX VOLUME

CLINICAL RATING OF ATTENTION

\[ \beta = 0.26, p = 0.025 \]
MAP-2 in midfrontal cortex of HIV+ cases with & 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><strong>Calbindin</strong></td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td><strong>Parvalbumin</strong></td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
</tbody>
</table>
Loss of calbindin interneurons is associated with cognitive impairment and memory loss in METH users patients with HIVE patients

HIV+ (control)                      HIVE+ METH-                      HIVE+ METH+

Calbindin immunoreactive interneurons

Heaton Global Score

Memory Score

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

r = -0.695, n=20, p<0.01.
Mechanisms of neurodegeneration mediated by HIV and METH

1. Oxidative stress
2. Excitotoxicity
3. Mitochondrial dysfunction
4. Alterations in calcium metabolism
5. Interference with signaling pathways of trophic factors
6. Cytokines, chemokines and other neuro-inflammatory factors
7. Increased viral load, replication, trafficking, altered viral resistance
METH-Dependence Exacerbates HIV-Associated Neuronal Injury

Chang et al, Am J Psychiatry 2005

Chronic METH: Additional Neuronal Injury (especially in Striatum)
METH-Dependence Exacerbates HIV-Associated Glial Response

CHANG et al Am J Psychiatry 2005

METH-Dependence Exacerbates HIV-Associated Glial Response

[CHO] (mmoles/kg)

- 1.75
- 2.25
- 2.75
- 3.25

Frontal WM
Frontal GM
Basal ganglia

[MI] (mmoles/kg)

- 4
- 6
- 8
- 10
- 12

Frontal WM
Frontal GM
Basal ganglia

SNN HIV                  ME TH                HIV+METH

(n=39)                (n=44)               (n=36)       (n=24)

* P < 0.05
** P < 0.005
METH-Dependence Exacerbates HIV-Associated Brain Injury

Chang et al. Am. J. Psychiatry 2005

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Frontal WM  Frontal GM  Basal ganglia

[CHO] (mmoles/kg)

METH  HIV  HIV+METH

(n=39)  (n=44)  (n=36)  (n=24)

*  P < 0.05
**  P < 0.005
***  P < 0.0001
METH associated with elevated biomarkers of inflammation

- METH users had higher levels of 5 markers of macrophage activation* in plasma
  - 3 were also higher in CSF
- Similar to HIV RNA, levels varied with recency of METH use
  - HIV-METH- lowest
  - METH+Utox- intermediate
  - METH+Utox+ highest

*MCP-1, sCD14, sTNFR-II, TNF-alpha, and MIP-1 beta
Relapse to METH Abuse or Dependence diagnosis during 12 month follow-up is associated with higher plasma HIV RNA (n=63)

Wilcoxon Rank Sums Test (Z = 11.45, p<.001)
Antiretroviral Drug Resistance

Methamphetamine is Associated with DR

- Resistance mutations were determined in 63 subjects enrolled in NIDA-funded projects
- 45% had resistance mutations for at least one antiretroviral
- Among METH dependent individuals, DR was associated with shorter durations of METH abstinence

Hightower et al, XIV International HIV Drug Resistance Workshop
Cofactors in HIV Associated Neurocognitive Complications

- Drug Abuse - example of methamphetamine
- **Coinfection with Hepatitis C [HCV]**
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments
HCV and the Brain

*Neurologic Syndromes*

- Hepatic encephalopathy
- Anterior optic neuropathy
- CNS vasculitis with ischemic or hemorrhagic strokes
- Cranial neuropathy
- Demyelinating myelitis
- Restless leg syndrome
- Cognitive/mood changes with Rx

Rate of Neurocognitive Impairment in HCV+ Persons in Anhui, China

% NP-impaired

HCV- (n = 147)

HCV+ (n = 51)

*** p < .001
HCV Confers Risk for Neurocognitive Impairment

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 Brains of Persons Dying of HIV

A-D Polyclonal antibody to HCV NS5A structural protein; E-H monoclonal anitbody to NS5A; I-L monoclonal antibody to HCV core antigen. B,F,J, C,G,K consistent with astrocytic localization; D,H,L consistent with macrophage localization

Letendre et al 2007 JID 196, 361-370
### Pattern of neuropsychological impairment according to risk factor

<table>
<thead>
<tr>
<th>Deficit</th>
<th>Meth</th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Retention</td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Attention/Working Memory</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Speed of Information Processing</td>
<td>?</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Visuospatial Functioning</td>
<td>?</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Motor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>++</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Slowing</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

- : effect
- : no effect
? : uncertain
<table>
<thead>
<tr>
<th>Deficit</th>
<th>Meth</th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Executive Functioning</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problem-Solving/Planning</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Cognitive Disinhibition</td>
<td>++</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Decision-making</td>
<td>+++</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td><strong>Frontal Systems Behavioral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disinhibition</td>
<td>++</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Apathy</td>
<td>-</td>
<td>++</td>
<td>?</td>
</tr>
<tr>
<td>Executive</td>
<td>+</td>
<td>++</td>
<td>?</td>
</tr>
</tbody>
</table>

- : effect, - : no effect, ? : uncertain
Cofactors in HIV Associated Neurocognitive Complications

- Drug Abuse - example of methamphetamine
- Coinfection with Hepatitis C [HCV]
- Aging
- Immune reconstitution syndrome
- Neurotoxic Treatments
Effects of Aging on expression of HAND

- cART prolonging survival: 15% now age > 50
- Does chronic HIV interact with aging related changes in brain?
- Sacktor et al., report increased executive dysfunction in older HIV+ with HAND in Hawaii cohort

Sacktor, et al. 2007 J Neurovirol
Older (>50) have approximately 10% greater rate of NP Impairment relative to age appropriate norms.
Figure 1. A photomicrograph (magnification x680) of intraneuronal staining of α-synuclein by immunocytochemistry, of neurons in the substantia nigra (A) and of neuritic staining in the temporal cortex (B). [courtesy I. Everall, et al., study of NNTC specimens]
Increased Frequency of \( \alpha \)-Synuclein in HIV

- Study of 73 substantia nigra in HIV infected individuals aged 55 years and more (also in temporal cortex in subset)
- 16% had \( \alpha \)-synuclein staining, compared with 9% reported in the literature

Everall, et. al. from a study of NNTC brains
NeuroAIDS and Comorbidities Summary

- HAND is prevalent in cART era
- Synaptodendritic Injury is a substrate
- Even though most persons with HAND are not grossly demented, life functioning can be affected
- Comorbidities such as drug abuse [eg. Methamphetamine] and coinfection [eg. HCV] may contribute to persistence of HAND
- Joint effects of HIV, Meth, and HCV may involve common immunoneuropathogenesis
- Aging may increase hazard of HAND or HIV may advance other age related brain changes
- cART effects on CNS need to be examined in context of these comorbidities
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<table>
<thead>
<tr>
<th>Project</th>
<th>Funding Agency(s)</th>
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<tr>
<td>HIV Neurobehavioral Research Center (HNRC)</td>
<td>NIMH (MH 62512)</td>
</tr>
<tr>
<td>CNS HIV Anti-Retroviral Effects Therapy Research (CHARTER)</td>
<td>NIMH NINDS (MH 22005)</td>
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<td>National Institute on Drug Abuse Program Project</td>
<td>NIDA (DA 012065)</td>
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<td>National NeuroAIDS Tissue Consortium (NNTC)</td>
<td>NIMH NINDS (MH 59745) (MH 59656)</td>
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Thank You!

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Interaction between age group and viral burden showing that levels of CSF HIV RNA differ according to NP impairment in older subjects but not in younger subjects.
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microglia</td>
<td>80%</td>
</tr>
<tr>
<td>Astroglia</td>
<td>?</td>
</tr>
<tr>
<td>Endothelial</td>
<td>10%</td>
</tr>
<tr>
<td>Neurons</td>
<td>0%</td>
</tr>
</tbody>
</table>
HIV-Associated Brain Damage Involves Neuronal Pathology

Synaptic Injury is Prominent
Cellular localization of HCV in macrophages and astrocytes in the brain

Demonstration of HCV-Immunostaining in the brain METH cases with HIVE.