NeuroAIDS in the modern treatment era

Igor Grant, MD,
Distinguished Professor and Chair
Department of Psychiatry
Director
HIV Neurobehavioral Research Program
University of California, San Diego

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HIV brain disease in the modern treatment era

- Although modern ARV treatment has markedly reduced brain disease from opportunistic infections, **HIV associated neurocognitive disorders (HAND)** remain prevalent, affecting about 40% of HIV+
- HAND still occurs in successfully treated [plasma HIV undetectable] individuals
- As HIV+ people survive longer, there may be increasing “brain burden” due to chronic inflammation which may amplify effects of
  - Age related metabolic, vascular, and neurodegenerative processes
  - Comorbidities, eg drug abuse, head injury, HCV, other coinfections
- HAND affects critical behaviors that are of public health concern
  - Medication adherence [transmission risk; resistance]
  - Risk behavior [transmission risk; superinfection]
  - Everyday functions, eg., driving [risk to self and others]
  - Reduced work efficiency; more unemployment [loss of productivity; personal and societal economic impact]
Prevalence of Specific HAND Diagnoses in CHARTER (N=1555 HIV+):

- **NPN** = neurocognitive normal
- **ANI** = asymptomatic neurocognitive impairment
- **MND** = mild neurocognitive disorder
- **HAD** – HIV associated dementia

54% NPN
35% ANI
9% MND
2% HAD

Heaton et al., Neurology 2010, 75(23): 2087-96
Neurocognitive Impairment by Domain in HIV+ from Pre-CART and Post-CART Eras

Percent Impaired

SIP=speed of information processing

* p<.05; ** p<.01; ***p<.001

Neuropathology of HIV in the pre-HAART era

HIV Encephalitis

Vacuolar myelopathy

Atrophy
white matter
pallor

Microglial Nodules
MNGC’s

HIV p24

Microgliosis
Astrogliosis

Severity of HIVE in the Pre-HAART era

% of total

HIVE mild
HIVE moderate
HIVE severe

No alterations
40%

Opportunistic infections or mixed
35%

HIVE
25%

Courtesy Eliezer Masliah, UCSD HNRP
Loss of synapses and dendrites in HIV+
Injury to synapses and dendrites may form a basis of HIV neurocognitive impairment

Progressive Dendritic Loss from No HAND (A) to Severe HAND (D)

Greater Cognitive Impairment Before Death Corresponds to Greater Dendritic Loss

HIV: from subacute to chronic disease

Pre-HAART

HIV replication in the CNS

Neuroinflammatory Response

Sub-acute HIVE

OPPORTUNISTIC Infections
Rapid progression to AIDS & death in ~ 5 yrs

HIV in the Brain

HAART

Latent HIV in the CNS?

Compartmentalization
Resistance mutations
Chronic neuroinflammation
Systemic metabolic disturbance
Neurotoxicity of ARV?

Chronic HIV disease

Long-term survival in well treated cases

Co-morbidities: Aging, Drugs, HCV

Courtesy Eliezer Masliah, HNRP UCSD
Neuropathology of HIV in the HAART era

(A) Severe white matter injury with astrogliosis (LFB). (B) Vascular infiltration in the white matter by macrophages (PAS). (C) Lymphocytic perivascular infiltration (H&E). (D) ‘Burnt-out’ form with neuronal atrophy (H&E). (E) Plaque-like lesions (anti-Aβ, 4G8). (F) Intra-neuronal Aβ (anti-Aβ, 4G8). Scale bar 35 um.

Courtesy Eliezer Masliah, HNRP UCSD
**What factors are associated with HAND?**

- **Viral factors**
  - Clade? Probably not
  - Higher molecular viral diversity in circulating HIV?
  - Shift in viral tropism, eg., to dual tropism? Maybe
  - Specific neurotropic/neuropathogenic variants? Unclear
  - ARV resistance?
  - Viral molecules, eg., Tat; gp120: contribute to abnormal intracellular signaling, protein mismanagement, and dendritic injury

- **Host vulnerability**
  - Unknown if specific host genetic factors confer neuro-vulnerability. Possibly APO E4
  - Co-morbidities may amplify HIV effects: substance abuse; HCV; head injuries; aging; metabolic syndrome

- **Treatment factors**
  - Treatment not begun early enough to prevent lasting brain injury?
  - Ineffective: not sustained suppression, particularly in CNS; persisting viral reservoirs?
  - Neurotoxicity of ARV?
Productive and latent forms of HIV in the brain can release viral proteins that

- activate apoptotic pathways
- dysregulate calcium homeostasis
- promote oxidative stress
- alter cell cycle signaling pathways such as CDK5, leading to protein phosphorylation and misfolding
- interfere with clearance pathways such as autophagy, leading to abnormal protein aggregation

These processes converge on a final common pathway leading to synaptodendritic injury

Courtesy Eliezer Masliah
UCSD HNRP
Increased neuritic alpha synuclein expression in brains of 55-65 year olds; accelerated age related “protein mismanagement” in brains of HIV+?

- Neuritic $\alpha$-synuclein expression (arrows) was found in 16% of the substantia nigra studied (12/73)

Khanlou et al., J Neurovirol; 2009;15(2):131-138
Mechanisms of neurodegeneration: Cyclin Dependent Kinase 5 (CDK5) activation and abnormal phosphorylation

HIV

- Aging
- Loss of growth factors
- CDK5 + p35 activation: Protein Quality Control failure
- Protein misfolding and aggregation
- SYN, Aβ, TAU, others
- Neurotoxins
- Inflammation
- Oxidative stress

CLEARANCE
- Proteosome failure
- Autophagy
- Proteolysis (Neprilysin)

Neurodegeneration

Courtesy Eliezer Masliah
UCSD HNRP
Specific increase in CDK5 and activator p35 expression in human brains with HIVE

Patrick et al Am J Pathol; Crews et al CDD 2012, 2013
Productive and latent forms of HIV in the brain can release viral proteins that

- activate apoptotic pathways
- dysregulate calcium homeostasis
- promote oxidative stress
- alter cell cycle signaling pathways such as CDK5, leading to protein phosphorylation and misfolding
- interfere with clearance pathways such as autophagy, leading to abnormal protein aggregation or premature degradation of essential proteins

Thereby contributing to synaptodendritic injury
Abnormal accumulation of autophagosomes in Tat treated mouse neuronal cells

Persistence of Neurocognitive Complications may be driven partly by comorbid factors

- Aging
- Metabolic Syndrome
- Drug and Alcohol Abuse
- Coinfections eg., Hepatitis C, CMV, toxoplasma, TB, etc
- Neurotoxicity of treatments
- History of Neurologic Insults, eg., head injury, that may increase vulnerability to neuroAIDS
Neurocognitive performance declines faster with age in HIV+ compared to HIV-.
Data from UCSD HIV Neurobehavioral Research Program.

Age Effect: p<.0001
HIV Effect: p<.0001
Interaction: p<.0001
Example of HIV and medical morbidity interaction on cognitive performance: attentional function worsens with greater insulin resistance in HIV+ but not HIV-

The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence for Brain damage? Neurocognitive Impairment (NCI)?</th>
<th>HIV X drug?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Well documented in long term alcoholics</td>
<td>maybe</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>Well documented in extensive users</td>
<td>yes</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Data are mixed. Animal and imaging data on potential damage not consistently supported by neurocognitive reports</td>
<td>uncertain</td>
</tr>
<tr>
<td>Heroin/opioids</td>
<td>Numerous reports with contradictory findings; Some human neuropath and preclinical work suggests neural injury. No systematic evidence for neurocognitive impairment</td>
<td>unknown</td>
</tr>
<tr>
<td>Sedative/hypnotics</td>
<td>NCI in chronic heavy users</td>
<td>unknown</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Data too fragmentary</td>
<td>unknown</td>
</tr>
<tr>
<td>Cannabis</td>
<td>Mixed neuroimaging findings; meta-analyses of studies on adults report weak to null effect on neurocognition in those who are not using at time of testing</td>
<td>no effect or possibly protective?</td>
</tr>
</tbody>
</table>
HIV and METH enhance each other’s neurotoxicity

- Increased rates of neurocognitive impairment in HIV+ METH+
- Marked reduction in interneurons in HIVE+ METH+

Rippeth, et al. 2004

Percent Impaired

HIV- Meth-  HIV+ Meth-  HIV- Meth+  HIV+ Meth+

Non-METH Abusing Group  METH Abusing Group

Calbindin

Parvalbumin

Comorbidities can amplify each other: Alcohol abuse is associated with poorer neurocognitive functioning in older but not younger HIV+.

Gongvatana et al., in prep, TMARC

*p < 0.01
### Opioid using HIV+ in Russia and China

<table>
<thead>
<tr>
<th></th>
<th>Russia HIV+/Opioid+</th>
<th>China HIV+/Opioid+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>30</td>
<td>204</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>34.6 (3.2)</td>
<td>33.7 (4.4)</td>
</tr>
<tr>
<td><strong>Education (years)</strong></td>
<td>10.6 (1.8)</td>
<td>9.5 (1.9)</td>
</tr>
<tr>
<td><strong>% Male</strong></td>
<td>100%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>CD4</strong></td>
<td>265 [134-386]</td>
<td>464 [345-692]</td>
</tr>
<tr>
<td><strong>HIV RNA (log_{10})</strong></td>
<td>4.5 [4.3-4.7]</td>
<td>3.9 [1.7-4.5]</td>
</tr>
<tr>
<td><strong>% Impaired based on 3 domains</strong></td>
<td>40%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Russia data based on 30 cases examined in “Russia R21” collaboration between Pavlov and UCSD TMARC (I. Grant, E. Krupitsky et al.). China data from 204 cases in China CDC-HNRP collaboration (S. Letendre, R. Heaton, F. Zhang et al.)
Rates of neurocognitive impairment are elevated in HIV+ opioid addicts in Russian sample. Are lower rates in China due to concurrent methadone treatment?

Russia data based on 30 cases examined in “Russia R21” collaboration between Pavlov and UCSD TMARC (I. Grant, E. Krupitsky et al.). China data from 204 cases in China CDC-HNRP collaboration (S. Letendre, R. Heaton, F. Zhang et al.).

*Uses US normative corrections.
Opioid partial/full agonists may inhibit chemokine CCL2-MCP1 induced monocyte migration; possible neuroprotective effect in HIV infection?

Cavallo et al., J Immunol; 2015; 194(7): 3246-3258
Comorbidities that may influence HAND: possible effects of latent CMV and toxoplasmosis

- **Bharti, et al., in prep**

**5A:** Higher CMV IgG levels were associated with worse GDS values.

**5B:** Higher anti-toxo IgG levels were associated with worse GDS values.
Have modern ARV regimens affected HAND?

• Yes: CNS opportunistic disease markedly reduced, eg., toxo, PML etc

• Yes: severe dementia has dropped from estimated 15% pre combination ART to <5% now

• BUT: moderate and mild forms of neurocognitive impairment remain prevalent
Early neurodamaging events? Reduced risk of HAND in those with absent history of severe immunosuppression and good virologic control

Heaton et al., Neurology; 2010; 75(23): 2087-96
Over repeated evaluations during several years, persons who remain chronically viremic are most likely to decline cognitively. Always Detectable decline > Sometimes Detectable or Always Undetectable (First visit to Last visit) with p = .005. 

Heaton et al., CID; 2015; 60(3): 473-480
Is there a “neurotherapeutic window”? Both high and low CSF Efavirenz associated with higher % of patients showing neurocognitive impairment

Letendre S, et al., HNRP data.
Could ART be implicated in cerebrovascular pathology: another link to HAND?

<table>
<thead>
<tr>
<th>% brain vessel pathology</th>
<th>NO HAART</th>
<th>YES HAART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild brain vessel path &amp; HAART</td>
<td>37%</td>
<td>62%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% HAND</th>
<th>Mild brain vessel path and HAND</th>
</tr>
</thead>
<tbody>
<tr>
<td>no brain vessel path</td>
<td>44%</td>
</tr>
<tr>
<td>mild brain vessel path</td>
<td>79%</td>
</tr>
</tbody>
</table>

Brain vessel pathology: Absent

Brain vessel pathology: Mild

Brain vessel pathology: Mod.-Sev.

Courtesy: V. Soontornniyomkij, HNRP
Specific neuroprotective agents? Not yet

Trials of various antioxidants, anti inflammatory drugs, etc have been largely negative

<table>
<thead>
<tr>
<th>Drug</th>
<th>Report</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selegeline</td>
<td>Dana <em>Neurology</em> 1998; Schifitto <em>Neurology</em> 2007</td>
<td>+/-</td>
</tr>
<tr>
<td>Thiocytic Acid</td>
<td>Dana Consortium <em>Neurology</em> 1998</td>
<td>no effect</td>
</tr>
<tr>
<td>Peptide T</td>
<td>Heseltine <em>Arch Neurol</em> 1998</td>
<td>-/+</td>
</tr>
<tr>
<td>Lithium</td>
<td>Letendre <em>AIDS</em> 2006</td>
<td>+</td>
</tr>
<tr>
<td>Memantine</td>
<td>Schifitto <em>AIDS</em> 2007</td>
<td>no effect</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Nakasuija <em>Neurology</em> 2013</td>
<td>no effect</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Simioni <em>Neurology</em> 2013</td>
<td>no effect</td>
</tr>
</tbody>
</table>

Possible new directions aimed at correcting processes of glutamate hyperexcitability [eg., nitromemantine] or CDK5 inhibitors [eg., sunitimib] are in proof of principle stage

Behavioral techniques, eg., cognitive retraining, exercise based interventions, might have value
Nitromemantine, which blocks extrasynaptic NMDA receptors, may promote synaptic integrity in study with gp120 transgenic mouse model of HIV

Summary

- HAND persists despite combination antiretroviral therapy (CART)
- Even milder HAND produces behavioral and functional impairments that are significant to the individual and society, thus of public health importance
- Synaptodendritic injury is one of the substrates of HAND.
- Causes of neuronal injury are likely multiple, including viral products, inflammatory molecules, disruption in trophic factors, disturbed protein management, brain small vessel pathology; these processes, incl. expression of viral products may persist despite apparent control of viral replication
- Comorbidities (eg. drug abuse) may increase risk of HAND, and its progression
Summary (cont.)

- HAND amplified by age related neurologic, vascular and metabolic changes. Comorbidities may further accelerate age related neurocognitive declines.
- Neurocognitive health best preserved in those who never have CD4 nadirs <200 and are currently virologically suppressed (implication: treat HIV as soon as possible).
- While continuous virologic suppression is associated with least likelihood of neurocognitive decline over time, ART neurotoxicity or vascular toxicity need to be considered.
- No currently accepted neurotherapeutics; need new concepts, and possibly novel delivery systems to brain.
- Non pharmacologic (eg., cognitive rehabilitation) strategies may have promise.
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Go Russia R21 Team!

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Thank you!

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