HIV Associated Neurocognitive Disorders in the era of modern CART

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Points to be covered

- HIV associated neurocognitive disorder (HAND) is common in HIV
- HAND persists even where combination antiretroviral therapy (CART) is available
- Significance of HAND: biological and functional correlates
- Cofactors (comorbidities) increase likelihood of HAND, and may influence progression
- Virologic control in CNS helps ameliorate HAND, but may not be fully effective in many cases
- ARV with higher CNS penetration-effectiveness (CPE) have some value, but must be balanced vs neurotoxicity
- Non pharmacologic (eg., cognitive rehabilitation) strategies may have promise
**HIV Neurobehavioral Disturbances**

**HIV Associated Neurocognitive disorders (HAND)**

- **Primary HAND**
  - Asymptomatic neurocognitive impairment
  - Mild neurocognitive disorder
  - HIV-associated dementia

- **Secondary HAND**
  - Infection
  - Neoplasia
  - Cerebrovascular
  - Nutritional
  - Treatment related

**Emotional & other behavioral**

- **New Onset**
  - Depression
  - Anxiety
  - Adjustment disorders
  - HIV mania
  - HIV psychosis

- **Pre-exist / recurrent / comorbid**
  - Mood disorders
  - Substance use disorders
  - Other mental disorders
Despite ARV benefits on morbidity and mortality HAND remains prevalent

ARV, antiretroviral; CDC, Centers for Disease Control; HAND, HIV-associated neurocognitive disorders

Prevalence of HAND in nonAIDS HIV+ has increased as people remain medically asymptomatic longer

NC Impairment by Domain in HIV+ Samples from Pre-CART and Post-CART Eras (NCI only)

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

HIV Associated Neurocognitive Disorders (HAND): Frascati Criteria

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

Antinori, et al., Neurology 2007
Frequency of Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) and HIV Associated Dementia (HAD) (from CHARTER Cohort)

- ANI: 72%
- MND: 21%
- HAD: 7%
Neurocognitive Impairment Matters

It can lead to problems in everyday functioning such as work inefficiency, driving impairment, and worse adherence to treatment.

Marcotte et al., 2004
Severity of NCI is Associated With Lower Health-related Quality of Life

HIV- (N=132) > HIV+ WNL (N=105) > ANI (N=34) > MND (N=25)

HIV- > HIV+WNL > ANI > MND

Woods SP: R01 MH73419
When everyday function is tested objectively, ANI and MND result in comparable deficit

Similar deficits in patients with asymptomatic neurocognitive impairment (ANI) and symptomatic impairment on neuropsychologic testing performance (mild neurocognitive disorder [MND] and HIV-associated dementia combined) in the University of California San Francisco (UCSF) HIV Over 60 Cohort (top). Similar deficits on functional performance among patients with ANI and MND (bottom). Adapted from Chiao et al 2013, 29(6):949-956.

Compared to Neurocognitively Normal (NCN) ANI Increases Risk for progression to Symptomatic HAND

NML: n=226
ANI: n=121

Relative Risk: 3.02
CI: 2.08, 4.42

% with no Daily Living Difficulties

Time (months)

p<.0001
Neurocognitive Change Status in CHARTER Sample with $\geq 4$ visits (n=436)

- Decline (n=98): 22.5%
- Stable (n=266): 61.0%
- Improve (n=72): 16.5%
HIV+ persons often have “comorbidities”, eg., HCV coinfection; drug abuse; prior head injuries, which can compound HIV effects on brain: Frequency and Severity of HAND rise with Comorbidities
Pathogenesis of HAND

1. Activated astrocytes increase permeability of BBB and promote migration of HIV-infected monocytes.
2. HIV-infected monocytes cross the BBB and become perivascular macrophages.
3. Activated perivascular macrophages and microglia replicate HIV-1 and express neurotoxic molecules (e.g., gp120).
4. Neurotoxic molecules activate astrocytes.
5. Increase in brain concentration of glutamate and neurotoxins results in neuronal injury.
6. HIV-associated neural injury leads to AF impairment.

Courtesy S.P. Woods, S. Letendre et al.
HAND associated with reduced N acetyl aspartate (NAA: an indicator of neuronal integrity) signal on MR spectroscopy and more white matter abnormalities on quantitated MRI

Fennema-Notestine et al. CROI 2013
Abnormal white matter signal is associated with HIV

Proton density  T 2

HIV-  HIV+

Abnormal White Matter

Courtesy T. Jernigan, HNRC
Abnormal white matter signal seen on quantitated MRI in about 1/3 of HIV+ cases

34.2% of sample (n = 301) have significant white matter abnormalities

Abnormal White Matter Cutoff

Jernigan, Fennema Notestine et al. CHARTER data
Increased mean diffusivity, suggesting injury to white matter tracts in NCI HIV+

Sample consecutive 5-mm slices showing voxels with significantly increased MD (in blue) in neurocognitively impaired (NCI) relative to unimpaired HIV+ participants, overlaid on white matter tract skeleton (green), and averaged FA image (grayscale). (Gongvatana, et al. INS 2008)
Reduced fractional anisotropy associated with more executive dysfunction

- Red highlights indicate significant positive, partial correlation clusters between executive domain T-score and fractional anisotropy (independent of age)

- Significant regions shown are genu, frontal association fibers, posterior limb of internal capsule

Jacobus et al., INS 2008
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

Disordered protein management may be another substrate of HIV neuropathogenesis: Perivascular and diffuse Aβ and neuritic plaques in brains

Soontornniyomkij and Achim, CNTN data
Comorbid factors:
Greater neurocognitive impairment with age in HIV+ vs HIV- persons

Grant et al CHARTER & HNRP data
Comorbid factors: Markers associated with metabolic syndrome are related to neurocognitive impairment

- Cross-sectional visits with “minimal” comorbidities
- Biomarkers of metabolic syndrome compared to global NP performance
- ROC curves identified thresholds associated with global NP impairment

Courtesy J.A McCutchan and S. Letendre
Comorbid factors: APO E4 HIV+ have worse neurocognition

Association of apolipoprotein (Apo) E4 with poorer neuropsychologic testing performance shown by Z scores in patients in the University of California San Francisco (UCSF) HIV Over 60 Cohort (adjusted for CD4+ cell count, nadir CD4+ cell count, years HIV seropositive, and plasma HIV RNA level). Adapted with permission from Atputhasingam et al 2013, Poster presented at Annual Scientific Meeting of Am Geriatrics Soc May 2-5.

Management of HAND requires consideration of multiple mechanisms: controlling HIV is 1\textsuperscript{st} step

- **Antiretrovirals**
  - Reduce HIV replication in the CNS
  - Improve neuroprotection
  - Reduce Neurotoxins and neuroinflammation
  - Cognitive health

Modified from S. Letendre
Lower neurocognitive impairment risk when immuno-suppression is avoided and virologic control is good

Heaton RK, et al. (2010). Neurology, 75, 2087-2096
Historical HIV neuromedical factors associated with white matter and gray matter damage

- Lower nadir CD4
  - abnormal white matter
  - white matter volume
  - subcortical gray matter
  - neuronal integrity (NAA)

- Longer exposure to ART
  - white matter, controlling for duration of HIV infection

Jernigan et al. JNV 2011; Fennema-Notestine et al. CROI 2013
Plasma VL Over Time vs. Summary NP Change Score

Heaton et al. CHARTER data

$p = .005$
CSF Viral Loads Are Associated with HAND When Compared to Plasma Viral Loads

Letendre et al, 17th CROI 2010, Abstract 172

Letendre et al, 16th CROI 2009, Abstract 484b
<table>
<thead>
<tr>
<th>CNS Penetration Effectiveness Ranks 2010</th>
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<tr>
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<td><strong>NRTIs</strong></td>
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<td>Zidovudine</td>
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<td>Emtricitabine</td>
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<td>Didanosine</td>
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<td><strong>NNRTIs</strong></td>
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<td>Nevirapine</td>
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<td><strong>PIs</strong></td>
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<td>Fosamprenavir-r</td>
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<td>Tipranavir-r</td>
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<td><strong>Entry/Fusion Inhibitors</strong></td>
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<td>Maraviroc</td>
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<tr>
<td>Enfuvirtide</td>
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<tr>
<td><strong>Integrase Inhibitors</strong></td>
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<td>Raltegravir</td>
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*Letendre SL, et al. 17th CROI 2010, Abstract 172*
Higher CPE values are associated with lower HIV RNA levels in CSF

Letendre S et al, 17th CROI 2010, Abstract 172

Letendre et al, 16th CROI 2009, Abstract 484b

Copyright S. Letendre, 2011
Well designed studies indicate higher CPE regimens benefit neurocognition

Median effect size

- [2] Longitudinal univariate regression (N=33, 2 visits)
- [3] Cross-sectional single score univariate comparison (N=97)
- [3] Cross-sectional multiple scores univariate comparison (N=97)
- [5] Longitudinal multivariate regression (N=31, 105 visits)
- [11] Cross-sectional single score univariate comparison (N=467)
- [15] Longitudinal multivariate regression (visits=3046)
- [16] Longitudinal univariate regression (N=185, 2 visits)

CPE, CNS Penetration-Effectiveness
From Cysique, Waters & Brew (Central Nervous System Antiretroviral Efficacy in HIV infection: A Qualitative and Quantitative Review. BMC Neurology: provisionally accepted).
Presented with permission of the author
Is there a “neurotherapeutic window”? Both high and low CSF EFV associated with more neurocognitive impairment

How should neuroeffective therapy be modified in aging HIV population?

- Age related changes in plasma and cerebrospinal fluid (CSF) pharmacokinetics of Tenofovir (TFV)

Non Pharmacologic approaches to HAND? ANI improves after 3 months of cognitive rehabilitation

LEGEND: clinical evolution discordant between the two groups: the experimental group showed an improvement differential at T1, this improvement does not occur in the control group, which instead show a worsening of neurocognitive performance compared to T0 to T1.

Livelli, et al., CROI 2013
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Livelli, et al., CROI 2013
HNRP Recommendations for Evaluating and Managing Suspected HAND

- **Question** patients about cognitive symptoms and activities of daily living at routine visits and before initiating ART
  - Brief testing improves the ability to correctly identify HAND
  - Screen for and treat other conditions that could account for nervous system complaints (e.g. co-infections, substance use, mood disorders, vascular disease, metabolic disorders)
  - Consider lumbar puncture and neuroimaging

- **Consider using ART with higher CPE** since accumulating data support that it better reduces HIV in CSF and leads to neurocognitive improvements

- **Continue to monitor** effectively treated patients
  - Cognitive impairment might persist or even occur for the first time in treated individuals: drug resistance and/or drug neurotoxicity?
Examples of assessment methods for HAND

**Symptom questionnaire**
- ‘3 questions’
- MOS-HIV
- PAOFI

**Screening tests**
- International HIV Dementia Scale
- Montreal Cognitive Assessment
- HIV Dementia Scale

**Brief NP testing**
- ALLRT Brief Neurocognitive Screen
- Grooved pegboard
- Action fluency
- Computerized testing (e.g. CogState)

**Comprehensive NP testing**
- At least 5 cognitive abilities
- At least 2 tests per ability

NP = Neuropsychological; MOS-HIV = Medical Outcome Study HIV Health Survey; PAOFI = The Patients Assessment of Own Functioning Inventory; ALLRT = AIDS Clinical Trials Group Longitudinal Linked Randomized Trials
**Revised EACS Guidelines: 3 questions**

Patients are considered to have an “abnormal” result when answering “yes, definitely” on at least one question

<table>
<thead>
<tr>
<th>Question</th>
<th>Never</th>
<th>Hardly ever</th>
<th>Yes, definitely</th>
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<tbody>
<tr>
<td>Do you experience frequent memory loss? (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)</td>
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<td>Do you feel that you are slower when reasoning, planning activities, or solving problems?</td>
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<tr>
<td>Do you have difficulties paying attention? (e.g. to a conversation, a book, or a movie)</td>
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Simoni et al. AIDS 2009
International HIV dementia scale

- **Memory:**
  - Word Recall

- **Motor speed:**
  - Finger tapping

- **Psychomotor speed:**
  - Alternating hand movements

### Memory-Registration
- Give four words to recall (dog, hat, bean, red) - 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. **Motor Speed:** Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.
   - 4 = 15 in 5 seconds
   - 3 = 11-14 in 5 seconds
   - 2 = 7-10 in 5 seconds
   - 1 = 3-6 in 5 seconds
   - 0 = 0-2 in 5 seconds

2. **Psychomotor Speed:** Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.
   - 4 = 4 sequences in 10 seconds
   - 3 = 3 sequences in 10 seconds
   - 2 = 2 sequences in 10 seconds
   - 1 = 1 sequence in 10 seconds
   - 0 = unable to perform

3. **Memory-Recall:** Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).
   - Give 1 point for each word spontaneously recalled.
   - Give 0.5 points for each correct answer after prompting
   - Maximum = 4 points.
Classification accuracy of the HIV Dementia Scale (HDS)

CHARTER study, N=1580

Brief neuropsychological testing

- Brief neurocognitive screen (ALLRT)
  - Trailmaking A & B
  - Digit symbol test
    - Sensitivity up to 65%
    - Specificity up to 84%
- Grooved pegboard
- Paced auditory serial addition test
- CogState

Lack of Comparable, Reliable Diagnostic Methods Impedes International NeuroAIDS Research and Treatment

Proportion Impaired

- Chennai India: 56%
- Pune India: 47%
- Anhui China: 37%
- Kampala Uganda: 31%
- APNAC: 12%

NC Impairment in International HIV+ Cohorts

Utilizes population specific norms
- US: 36%
- Anhui: 35%
- Yunnan AIDS: 39%
- Zambia: 35%

Utilizes small normative sample or norms from another country
- Brazil: 62%
- Romania: 48%
- South Africa: 29%
HIV Effect Size Across Countries

Utilizes population specific norms

Utilizes small normative sample or norms from another country
Summary

- HIV associated neurocognitive disorder (HAND) is common in HIV
- HAND persists even where combination antiretroviral therapy (CART) is available
- Significance of HAND: biological and functional correlates
- Cofactors (comorbidities) increase likelihood of HAND, and may influence progression
- Virologic control in CNS helps ameliorate HAND, but may not be fully effective in many cases
- ARV with higher CNS penetration-effectiveness (CPE) have some value, but must be balanced vs neurotoxicity
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Priorities and Future Directions

- **HIV Reservoirs in the CNS**: research into timing, location and quantification of nervous system infection; whether viral evolution is compartmentalized, and whether it can be transmitted or eliminated.

- **Pathophysiology**: research into systemic and neurological inflammation and neurodegeneration; cerebrovascular disease; effects of aging and drug use.

- **Biomarkers**: research into imaging of viral reservoirs and ongoing disease activity; CSF-based biomarkers including state of the art “omics”; and the movement of biomarkers into clinical practice.

- **Clinical Studies**: research in acute and early infection; psychiatric manifestations; the development of specialized cohorts (e.g., women, children, drug abusers, other comorbidities); research into peripheral neuropathy; the integration of neurological and psychiatric complications with medical complications of HIV infection; pediatric studies to include children exposed to HIV but not infected; research into unique vulnerabilities in international settings, eg., effects of systemic inflammation due to TB, malaria, etc.

- **Development of CNS Specific Therapeutics**: research into targets for neuroinflammation; neuroprotection; antiretrovirals and elimination of CNS viral reservoirs; palliative care of persons with HAND or neuropathic pain; and CNS specific opportunistic infections (PML and TB). Development of cognitive remediation and other behavioral strategies.
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- Allen McCutchan

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- ...Drug Abuse
- ...Neurological Disorders and Stroke

Pharma
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