HAND is Common and Important in Patients on ART

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Points to be covered

- How is HAND diagnosed?
- How prevalent is it?
- What are the effects of ARV:
- Significance of HAND: biological and functional correlates
- What about ANI? If it is asymptomatic, does it matter?
- Is the whole thing a statistical artifact?

Grant I, et al., In Preparation
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

Prevalence of HAND
Prevalence of Specific HAND Diagnoses in CHARTER (N=1555 HIV+):

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

Heaton et al., Neurology 2010, 75(23): 2087-96
How have modern ARV regimens affected HAND?
Despite ARV benefits on morbidity and mortality HAND remains prevalent

Impaired individuals (%)

- Grant (1987)
- HNRC-500 (1995)
- CHARTER (2010)

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

The prevalence of HAND increases as persons with HIV remain medically asymptomatic for longer.

CART = combined antiretroviral therapy

HAND Diagnoses by Viral Suppression Across 2 Visits (n=618)

Always Suppressed
- NPN: 58%
- ANI: 21%
- MND: 17%
- HAD: 4%
- n=212

Sometimes Suppressed
- NPN: 70%
- ANI: 15%
- MND: 14%
- HAD: 1%
- n=159

Never Suppressed
- NPN: 63%
- ANI: 19%
- MND: 14%
- HAD: 4%
- n=247

CHARTER Data
## Viral Suppression Across to Visits: Demographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Always Suppressed</th>
<th>Sometimes Suppressed</th>
<th>Never Suppressed</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>212</td>
<td>156</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>45.9 (8.0)</td>
<td>42.8 (9.1)</td>
<td>42.5 (8.6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>12.9 (2.5)</td>
<td>13.1 (2.4)</td>
<td>12.8 (2.6)</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>%Male</td>
<td>77%</td>
<td>82%</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>%Female</td>
<td>23%</td>
<td>18%</td>
<td>21%</td>
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<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
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<tr>
<td>% Afr. Am.</td>
<td>37%</td>
<td>45%</td>
<td>44%</td>
<td></td>
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<tr>
<td>% Cauc.</td>
<td>51%</td>
<td>42%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>% Hisp.</td>
<td>11%</td>
<td>9%</td>
<td>12%</td>
<td></td>
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<tr>
<td>% Othr.</td>
<td>1%</td>
<td>4%</td>
<td>3%</td>
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Viral Suppression Across to Visits: Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Always Suppressed</th>
<th>Sometimes Suppressed</th>
<th>Never Suppressed</th>
<th>p-value</th>
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<tbody>
<tr>
<td><strong>n</strong></td>
<td>212</td>
<td>156</td>
<td>247</td>
<td></td>
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<tr>
<td>% AIDS</td>
<td>72%</td>
<td>63%</td>
<td>51%</td>
<td>&lt;.0001</td>
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<tr>
<td>Est. Duration HIV+ (years)</td>
<td>12.1 [6.5-16.0]</td>
<td>10.9 [2.4-16.0]</td>
<td>8.8 [3.6-14.8]</td>
<td>0.0013</td>
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<tr>
<td><strong>ART Status</strong></td>
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<tr>
<td>HAART</td>
<td>98%</td>
<td>86%</td>
<td>48%</td>
<td>&lt;.0001</td>
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<tr>
<td>No ARVs</td>
<td>1%</td>
<td>9%</td>
<td>22%</td>
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<tr>
<td>ARV Naive</td>
<td>0%</td>
<td>5%</td>
<td>30%</td>
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</table>
Stability of Viral Suppression Over 3 Visits (n=334*)

- Always Suppressed: 44%, n=147
- Sometimes Suppressed: 38%, n=127
- Never Suppressed: 18%, n=60

* All participants were stably on ART; limit of detection = 50 copies/mL

CHARTER Data
Does HAND matter?
HAND associated with reduced neuronal integrity and more white matter abnormalities

HAND classification (Normal vs. HAND) best predicted by FGM NAA and abnormal white matter

Fennema-Notestine et al. CROI 2013
Likelihood of HIVE according to Antemortem NP Status

Cherner M, et al., Neurology; 2002;59(10),1563-7
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., Neurology 2004, 63 (8): 1417-22
ASYMPTOMATIC NEUROCOGNITIVE IMPAIRMENT (ANI): Does it Matter?
Prevalence of Specific HAND Diagnoses in CHARTER: (NCI Only)

Heaton et al., Neurology 2010, 75(23): 2087-96
ANI is associated with worse simulated driving performance

Marcotte et al., in preparation

HIV+ NP Normal (n = 67)
ANI (n = 31)

*** p < .001  * p < .05  + p < .10
Mortality by HAND Diagnosis: 543 cases from the National NeuroAIDS Tissue Consortium

Rooney A, et al. In Submission
Frontal Gray Matter NAA by HAND Status

Frontal Gray Matter NAA (mean/SE absolute measure)

HAND Status

NPN  ANI  MND  HAD

CHARTER Data
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

% Area Occupied by Dendrites

Many clinicians agree that MND, which requires both neurocognitive impairment and decline in everyday functioning, has clinical significance (eg., see EACS guidelines). But the ascertainment of functional impairment can be challenging.
Agreement between self report (SR) and performance based (PB) functional measures

- Agree: No Functional Impairment (n=156)
- Agree: Functional Impairment (n=20)
- Disagree: Impaired by Self-report Only (n=37)
- Disagree: Impaired by Performance-based Only (n=20)

Assessment of function: HAND diagnoses based on self report (SR) and performance based (PB) data

- SR: n=192, n=40, n=1
- PB: n=177, n=47, n=9
- SR+PB: n=137, n=84, n=12

ANI is associated with reduction in self-awareness of impairment

Performance on the NAB across diagnostic groups

Discrepancy between performance and self-assessment of performance measured post-testing

Individuals with ANI and MND had greatest discrepancies driven by poorer performance

Performance-based Functional Impairment by HAND Diagnosis

- **Vocational Assessment***
- **Med Management**

% Impaired

- **NML**
- **ANI**
- **MND**
- **HAD**

*Valpar Work Sample; CHARTER Data
ANI Increases Risk for Symptomatic HAND: Self-report or Performance-based

Total Sample

- NML: n=226
- ANI: n=121
- Relative Risk: 3.02
- CI: 2.08, 4.42
- p<.0001

Virologically Suppressed

- NML: n=85
- ANI: n=55
- Relative Risk: 3.1
- CI: 1.7, 5.7
- p<.0001

Grant I, et al., In Preparation
If we cannot treat HAND why bother diagnosing it? Why worry people?

- In general this seems somewhat nihilistic. Historically there were few conditions that Medicine diagnosed that had good treatments initially. Indeed, effective treatments are predicated on accurate diagnosis and systematic assembly of clinical data.

- In our experience, discussing with patients that they may have cognitive challenges actually helps them understand why they may not have been “up to par” and opens avenues for dealing with cognitive compromise; and does not cause undue anxiety.

- While it is true that ARV and non ARV pharmacological treatments have shown only modest benefit at best, even modest improvements may be very meaningful to patients.

- Some preliminary evidence suggests cognitive training approaches may be helpful.
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 from T0 to T1.

Livelli, et al., CROI 2013
ANI more amenable to memory rehabilitation strategies than MND/HAD

<table>
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<tr>
<th>Condition</th>
<th>NP Normal (n=44)</th>
<th>ANI (n=5)</th>
<th>MND/HAD (n=5)</th>
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<tr>
<td>Paired Associate Learning Task score</td>
<td>Hedge's $g_s$</td>
<td></td>
<td></td>
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<tr>
<td>Control condition</td>
<td>1.02</td>
<td>0.94</td>
<td>0.41</td>
</tr>
<tr>
<td>Self-generated condition</td>
<td>Hedge's $g_s$</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>NP normal: 1.02</td>
<td>ANI: 0.94</td>
<td>MND/HAD: 0.41</td>
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</tbody>
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Woods SP : R01 MH73419
If 15-20% of HIV uninfected persons score mildly “impaired” on Neurocognitive Testing, does it not mean it is all a statistical artifact?

Not necessarily!
Why might someone score in the neurocognitively impaired range?
Neurocognitive Impairment Reliability on Retesting

- We examined the test-retest reliability of neurocognitive impairment (NCI) among HIV- controls tested twice approximately one year apart.
- If NCI diagnostic is random, then cross-classification of the diagnostic in test-retests should be consistent with random assignment (i.e., the 15-20% impaired at time 2 should be a random sample and not typically be the same people as were impaired at time 1).
- Instead, we find very strong evidence that NCI diagnostic as used in HAND is informative and with substantial test-retest reliability.
Stability of Impairment: HNRC Study HIV-Controls

- 117 HIV- controls
- Odds of impairment at time 2
  - If impaired at time 1: 13/8 = 1.625
  - If not impaired at time 1: 5/91 = 0.055
- OR = 29.6, 95% CI (8.94, 114.4), p-value < 0.001
- Cohen’s kappa = 0.603 (substantial)
Conclusions

- HAND can be reliably diagnosed. To avoid misclassifications, repeat assessment of initially impaired cases is advisable.
- HAND is associated with worse everyday functioning, therefore has significance to the patient.
- Converging evidence indicates HAND has neurobiological underpinnings, and may influence mortality.
- Diagnosing MND based on self report only may underestimate its occurrence.
- There are no reliable ARV or non ARV medications for HAND; however, if we assess for HAND systematically, particularly in clinical trials, new therapeutic insights may emerge.
- The apparently high rate (15 – 20%) of NCI in HIV- controls does not mean it is a statistical artifact; for most HIV- people the NCI is a reliable finding, perhaps reflecting mild TBIs, developmental issues, etc.
- In HIV+ the rate of NCI is typically double that of HIV-. This indicates that there is an HIV effect, over and above background events.
**Acknowledgment**

- We would like to thank all of the volunteers and investigators who participated in the studies listed below:

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<td>NIMH/NINDS</td>
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<tr>
<td>Hansa 2013 meeting</td>
<td>Abvie</td>
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Thank you for your attention

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