Diagnosis and Monitoring of HAND

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Disclosures:
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DSM-5 and HAND

• “Major Cognitive Disorder” vs HAD

• “Minor Cognitive Disorder” vs MND
### AAN Criteria for HAD

- At least moderate NP impairment (> 2 SDs below the appropriate normative mean) on at least 2 neurocognitive domains
- At least moderate functional decline (> 2 sds below mean) on a standardized test, if available
- Neither NP impairment nor functional decline may be explained by confounding conditions

### Frascati Criteria and DSM-5

**What’s the Difference?**
- DSM-5 is not pathogen specific
- DSM-5 does not require deficits in 2 domains
- “Minor” neurocognitive disorder is not “minor” to the patient
- “Independence” is the only area of functional focus
- DSM-5 defines a limited exclusionary work-up
- DSM-5 has no analogue for ANI

### Frascati Criteria Vs the DSM-5

- The Frascati Criteria are the revised AAN criteria for what were then referred to as “HIV-associated cognitive-motor disorder” from 1991
- The Frascati Conference took place in 2005
- The Frascati diagnostic criteria were published in 2007
- DSM-5 was published in 2013
Systemic Treatment Foci

- Suppression of plasma viral load to non-detectable levels
- Increase in number of CD4 cells
- Functional immune reconstitution
- Monitoring antiretroviral resistance using genotypic and phenotypic assays

HIV Associated Neurocognitive Disorder (HAND)

- HIV-Associated Dementia (HAD)
- Mild Neurocognitive Disorder (MND)
- Asymptomatic Neurocognitive Impairment (ANI)
- No NCI/ Potential for Neuroprotection

Diagnostic Criteria for MND

- Based on NP testing – not Sxs
  - At least mild NP impairment
    (>1 SD below a demographically appropriate normative mean), involving ≥ 2 cognitive domains
- Reported or demonstrated mild functional decline
- Not explained by confounding conditions
Diagnostic Criteria for Asymptomatic Neurocognitive Impairment (ANI)

- Presuming NP and Functional Status Testing are available:
- NP impairment of at least 1.0 sd but < 2 sd in ≥ 2 cognitive domains
- No reported or demonstrated functional decline
- Not explained by opportunistic CNS disease, systemic illness, psychiatric illness, substance use disorders, or medications with CNS effects

Frascati Criteria for HAND

<table>
<thead>
<tr>
<th>HIV-Associated Dementia</th>
<th>2 SD ≥ 2 Domains</th>
<th>Moderate to Severe Functional Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Neurocognitive Disorder</td>
<td>1 SD ≥ 2 Domains</td>
<td>Mild Functional Impairment</td>
</tr>
<tr>
<td>Asymptomatic Neurocognitive Impairment</td>
<td>1 SD ≥ 2 Domains</td>
<td>No Functional Impairment</td>
</tr>
</tbody>
</table>
Screening for HAND
50% prevalence across levels of HAND with patients stable on antiretroviral therapy (ART)
Neurocognitive impairment (NCI) predicts morbidity & mortality
ALL levels of impairment predict mortality
Cognition is a critical component for adherence and functional status

HAND Screening
• Several screening tests are available to use for referral to NP testing OR classifying impairment
• Currently, there are no clearcut data favoring any single specific screening instrument for HAND to classify impairment successfully
• Both critical and meta-analytic reviews suggest that there are still limitations to current screening instruments
• Future research may best focus on additions of specific NP tests to current screening instruments to increase accuracy across HAND, particularly ANI

HIV Dementia Scale (HDS)
• Antisaccadic Eye Movement Errors Can be eliminated from scale in the “modified HDS”
• Timed Alphabet (if able to say alphabet; otherwise, use numbers 1-26)
• Verbal Memory (with cueing) - recall should be at 5 min.
• Cube Copy time (“as precisely and quickly as possible”)
Limitations of the HDS

- HDS has issues with validity across cultures (inside and outside the USA)
- Few Hispanics
- Standardized on predominantly young males with higher educational level
- Most sensitive to more severe impairment
- ARV regimens were pre-Highly Active Antiretroviral Therapy (HAART)
- HAND is now milder post-HAART – with ANI > MND > HAD

International HIV Dementia Scale (IHDS)

- HDS issues with validity across cultures (inside and outside the USA)
- IHDS:
  - Finger Tapping for Motor Speed
  - Psychomotor Speed: Non-dominant hand coordination/speed (1: clench hand in fist on flat surface; 2: put hand flat palm down; 3: put hand perpendicular on side of 5th digit)
  - Verbal Memory

Montreal Assessment of Cognitive Impairment (MoCA)

- Rapid screen of 11 items requiring about 20 minutes; Normal: ≥26 of 30
- Includes Trail Making Test (TMT-B) and Dementia Scale (DS) (forward and backward) as well as verbal memory
- Abstraction, object naming, clock draw and language not frequently related to HIV infection
- Less data specifically demonstrating validation for HAND
EXIT Interview

- Long for screening test at 25 items
- Includes many neuro exam items
- Requires more training
- Strong correlation with full battery
- Overlaps IHDS on Luria Hand sequence II
- Has been tested in HAND, less sensitive than HDS but ↑ specificity

Screening for HAND by Self Report

Medical Outcome Study-HIV Cognitive Functional Status Scale

1. Difficulty reasoning and solving problems?
2. Forget things that happened recently?
3. Trouble keeping your attention on any activity for long?
4. Difficulty doing activities involving concentration and thinking?

Validated against NP overall performance in the Netherlands

Reviews of HAND Screening

- Haddow et al. (2013) retrieved 15 studies of the HDS, 10 of the IHDS, and 1 of both scales.
  - North America: 13 HDS studies
  - Sub-Saharan Africa: 7 IHDS studies
- Estimates of accuracy: Highly heterogeneous for the HDS but less so for the IHDS
Reviews of HAND Screening Issues
Is It Time to Rethink How NP Tests Are Used to Diagnose Mild Forms of HAND? Impact of False+ Positive Rates on Prevalence and Power

- False+ frequencies of 2–74% were observed for ANI/MND and 0–8% for HAD
- They recommend changing the Z score threshold to $\leq -1.5$ sds for mild cognitive impairment
- Limiting testing to 3–5 domains
- Using the average Z score to define an abnormal domain


• HIV-Associated Neurocognitive Disorders Remain Diagnoses of Exclusion

Increased Diagnostic Focus on Exclusion Criteria

- CNS infections or tumors
- Systemic Illness (metabolic sources)
- Prescribed medication/substance toxicities
- Developmental disorders
- Traumatic brain injury
- Depressive disorders
- Non-HIV-1-associated neurological disorder
MRI or CT Scan of Head

• Rule Out CNS Toxoplasmosis
• Rule Out CNS Lymphoma
• Typical to note with HIV:
  • Ventricular Enlargement
  • T2 Weighted Image Hyperintensities
  • Unidentified Bright Objects (UBOs)

Lumbar Puncture

• Cryptococcal Antigen
• VDRL (Syphilis)
• PCR (Polymerase Chain Reaction Virus)
  • JCV (John Cunningham virus)
  • EBV (Epstein Bar virus)
  • CMV (Cytomegalovirus)
  • HIV

Metabolic Sources

• Renal
• Hepatic (e.g., Hepatitis C Virus with or without metabolic effects)
• Pulmonic
Toxicities

• Dyslipidemia/CVA risk
• EFV (Efavirenz)
• ZDV (Zidovudine)
• Interferon-alpha
• Corticosteroids
• Substance Use

Implications for HAND Dx

• If there is a + screen for HAND, this means that the patient has NCI
• HAND is a different construct from NCI and HAND has its own criteria unrelated to NCI
• This leads us to the need to consider the diagnostic criteria for HAND

Accuracy of the Neurocognitive HIV study (NEU) Screen for Detecting Cognitive Impairment in Virologically Suppressed HIV+ Patients Muñoz-Moreno et al.; CROI 2014

This study assessed the utility of the NEU Screen for neurocognitive impairment including 3 paper-based NP tests (TMT-A and B and the Controlled Oral Word Association Test COWAT), having an expected administration time of ≤ 10 min.

• All Ss had data on a comprehensive battery of NP tests linked with clinical and demographic info.
• Sensitivity and specificity analyzed to assess the utility of the NEU Screen in detecting NCI. Logistic regression was used to analyze clinical and demographic variables linked to the classification.
Results: Subjects were mostly men (81%), with a Mdn age of 43 yrs, current CD4 count= 522 cells/mm3, CD4 nadir of 188 (80,285) cells/mm3, with 73% HCV negative.

- The rate of NCI was 52% and appeared significantly associated with time since HIV diagnosis (p=0.01), lower CD4 nadir (a trend), and existence of comorbidities.
- When the combination of scores included in the NEU Screen was analyzed for the detection of NCI, the sensitivity (95% CI) observed was 73.1% (62-82%), specificity 74.3% (63-83%), positive predictive value 75.9% (65%-85%), and negative predictive value 71.4% (60%-81%).
- According to logistic regression models, the correct classification of NCI by the NEU Screen was unrelated to any relevant demographic or clinical variable.

Conclusions: The NEU screen was judged to confirm fairly high sensitivity and specificity to detect NCI and may be useful specifically in virologically suppressed HIV+ persons

Next Step: ROC Model analyses to establish cut-off would further the current analyses.

Thoughts on HAND Screening Research
Several screening tests are available
Currently, there are no clearcut data for any single specific screening instrument
Both critical and meta-analytic review studies suggest that there may be limitations to the use of the current screening instruments
Future research may best focus upon how additions of specific NP tests to current screening instruments might increase accuracy across HAND, particularly in ANI

Neurocognitive Treatment Targets
- HIV-1 Associated Dementia (HAD) Complex ← formerly ADC
- HIV-1 Associated Minor Cognitive- Motor Disorder (MCMD)/MND
- Subclinical HIV-1 Associated Neuropsychological Impairment/ANI
- No Neuropsychological Impairment/ Neuroprotection
Neuroprotection

- No criteria have been developed for neuroprotective treatment
- Not considered an indication for effective ART
- More research needed!!!

Frascati Criteria and DSM-5
What's the Difference?

- The specificity of HAND to HIV is lost
- Once again, there will be a lack of parallel in research diagnostic criteria
- This could create issues with diagnostic reliability and validity for HAND and inconsistencies in research findings

Monitoring of HAND
HIV Associated Neurocognitive Disorder

• What happens in the Brain?

Latent Viral Infection in Brain

• Brain has been cited as an "HIV reservoir" in the setting of effective Era of Effective ART in periphery
• HIV proviral load in peripheral blood mononuclear cell (PBMC) has been associated with HAD
• To what extent is latent HIV a contributor to the pathophysiology itself?

Hypothetical Implications of HIV Life Cycle for CNS

• Possible role for viral proteins, some of which are neurotoxic, rather than whole virion burden taken alone
• Tat, gp120, Vif, Nef, Vpr, gp41, p24, Rev
• Impact of the protease inhibitors in the era of effective ART – depends on CNS penetration vs. accumulation of viral proteins and vascular toxicity
Neuronal Apoptosis

- Brain is predominantly a post-mitotic tissue
- Impact of apoptosis in brain:
  - Cell loss
  - Clinical Dysfunction
- No compensatory, salutary effect of apoptosis in brain as opposed to lymphocyte proliferation

Viral Proteins and Neuronal Apoptosis

- A focus on Tat and gp120
  - Share apoptotic pathways to specific mitogen-activated protein kinases: c-Jun vs. p38
  - However, studies show no correlation between overall neuronal density and

History of Neurocognitive Disorder
HIV-1 Encephalitis
HIV-1 Associated Dementia

Other Cells Than Neurons Are Involved in HIV-1 Brain Infection

- Monocytes
- Macrophages
- Microglia
- Astrocytes
- Inter-cellular cross-talk by cytokines and chemokines
Limited Value of CSF Viral Load Monitoring in the Era of Effective ART

- Invasive, painful, and not a direct window to brain tissue
- Frequently non-detectable
- What about neuroimaging?
  - MRI
  - Volumetrics
  - FLAIR MRS

Magnetic Resonance Spectroscopy (MRS)

- Sensitive to effects without structural change; shows effects of HIV and aging
- Diagnostic utility (e.g., Progressive Multifocal Leukoencephalopathy {PML} versus HAD)
- Monitoring of cognitive impairment progression by region
- Monitoring of drug treatment response

HAND is a Global Problem
HAND is Common in the U.S.