Approach to HIV Associated Neurocognitive disorders (HAND)

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Overview

Neurobiology
Classification of HANDs
Epidemiological evidence to use HAART

- Screening tools
  Brief neuropsychiatric batteries
  Treatment of HANDs
Primary CNS Infection by HIV

- Asymptomatic neurocognitive impairment
- Minor neurocognitive disorder
- HIV-associated dementia
- Delirium
- Aseptic meningitis
- Vacuolar myelopathy
- Psychotic and mood disorders due to a general medical condition
Secondary CNS Diagnoses Due to Systemic Immunosuppression

- Non-viral opportunistic infections
- Viral opportunistic infections
- Neoplasms
- Cerebrovascular disorders

B. Peripheral nervous system disorders
HIV neuropathogenesis

- HIV does not infect neurones and oligodenrocytes but the monocytes, microglia, astrocytes and endothelial cells.
- Once in the CNS the virus persist and evolves into different strains independent of the systemic reservoir.
- HIV is not evenly distributed in the CNS. It has a predilection for the basal ganglia.
- CSF HIV RNA levels do not correlate with the peripheral circulation, especially in the advanced stages.
### NIMH Panel Diagnostic Classification of HAND

| ANI | Acquired impairment in cognitive functioning, involving ≥ 2 ability domains, documented by performance of ≥ 1 standard deviation below the mean for age/education-appropriate norms on standardized neuropsychological tests, including  
|     | • Verbal/language  
|     | • Attention/working memory  
|     | • Abstraction/executive  
|     | • Memory (learning, recall)  
|     | • Speed of information processing  
|     | • Sensory perceptual, motor skills  
|     | Impairment does not interfere with everyday functioning  
|     | Impairment does not meet criteria for delirium or dementia  
|     | No evidence of another preexisting cause for the ANI |

| MND | Acquired impairment in cognitive functioning, as defined for ANI above  
|     | At least mild interference in daily functioning, including ≥ 1 of the following  
|     | • Self-reported reduced mental acuity, inefficiency in work, homemaking or social functioning  
|     | • Observation by knowledgeable others of at least mild decline in mental acuity, resulting in inefficiency at work, homemaking or social functioning  
|     | Impairment does not meet criteria for delirium or dementia  
|     | No evidence of another preexisting cause for the MND |

| HIV-1 associated dementia | Marked acquired impairment in cognitive functioning, involving ≥ 2 ability domains (typically, multiple domains), especially in learning new information, slowed information processing, and defective attention/concentration  
|                          | Impairment must be ascertained by neuropsychological testing with ≥ 2 domains 2 standard deviations or greater than demographically corrected means  
|                          | Marked interference with day-to-day functioning (work, home life, social activities)  
|                          | Does not meet criteria for delirium (e.g. Clouding of consciousness not a prominent feature)  
|                          | or  
|                          | If delirium is present, criteria for dementia need to have been met on a previous examination when delirium was not present.  
|                          | No evidence of another, preexisting cause for the dementia (e.g. Other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurological disease, or severe substance abuse) |

HIV Dementia
marked cognitive impairment with marked functional impairment

Minor Cognitive/Motor Disorder
cognitive impairment with mild functional impairment

Neuropsychological Impairment
abnormality in two or more cognitive abilities

Neuropsychological Deficit
clear abnormality in one cognitive ability
| **ANI** | Acquired impairment in cognitive functioning, involving ≥ 2 ability domains, documented by performance of ≥ 1 standard deviation below the mean for age/education-appropriate norms on standardized neuropsychological tests, including  
- Verbal/ language  
- Attention/ working memory  
- Abstraction/ executive  
- Memory (learning, recall)  
- Speed of information processing  
- Sensory perceptual, motor skills  
Impairment does not interfere with everyday functioning  
Impairment does not meet criteria for delirium or dementia  
No evidence of another preexisting cause for the ANI |
| **MND** | Acquired impairment in cognitive functioning, as defined for ANI above  
At least mild interference in daily functioning, including ≥ 1 of the following  
- Self-reported reduced mental acuity, inefficiency in work, homemaking or social functioning  
- Observation by knowledgeable others of at least mild decline in mental acuity, resulting in inefficiency at work, homemaking or social functioning  
Impairment does not meet criteria for delirium or dementia  
No evidence of another preexisting cause for the MND |
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Marked interference with day-to-day functioning (work, home life, social activities)  
Does not meet criteria for delirium (eg. Clouding of consciousness not a prominent feature)  
or  
If delirium is present, criteria for dementia need to have been met on a previous examination when delirium was not present.  
No evidence of another, preexisting cause for the dementia (eg. Other CNS infection, CNS neoplasm, cerebrovascular disease, preexisting neurological disease, or severe substance abuse) |
6 domains to be assessed

- Attention-information processing;
- Language;
- Abstraction-executive;
- Complex perceptual motor;
- Memory
- Sensory perceptual/motor skills
Asymptomatic neurocognitive impairment (ANI)

- 1 SD
- Two domains
- No impairment
Minor neurocognitive Disorder

Old definition: Two or more of the following for $\geq 1$ month:
- Impaired attention or concentration
- Mental slowing
- Impaired memory
- Slowed movements
- Incoordination
- Personality change, irritability or emotional lability

New definition: 2 domains, 1 SD, mild impairment
HIV Associated Dementia

- **Old definition:** Acquired abnormality in at least two of the following cognitive abilities for at least one month:
  - Attention/concentration
  - Speed of information processing
  - Abstraction/reasoning
  - Visuospatial skill
  - Memory/learning
  - Speech/language

**New definition:** 2 domains, 2 SD, marked impairment
<table>
<thead>
<tr>
<th>Level of impairment</th>
<th>Asymptomatic Neurocognitive impairment (ANI)</th>
<th>Minor neurocognitive disorder (MND)</th>
<th>HIV- dementia (HAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of impairment</strong></td>
<td>none</td>
<td>Mild everyday activities: reduced mental acuity, inefficiency in work, homemaking or social activities</td>
<td>Marked impairment in day-to-day activities at work, home or social functioning</td>
</tr>
<tr>
<td><strong>Number SD below population norm on neuropsychological test</strong></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Number of domains impaired</strong></td>
<td>2 (Attention/working memory; verbal/language; Abstraction/executive; Complex perceptual motor; Memory (learning and recall); speed of information processing; Sensory perceptual/motor skills)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria</strong></td>
<td>Absence of criteria for delirium or other causes for dementia. These conditions cannot be explained by another cause which conditions neurocognitive decline</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Significance of NCI

- ARVS decrease incidence
- Better QoL
- Improved Adherence
- Poor prognostic sign
- HIV-D- WHO stage 4 disease- Qualify for ARVs
HIV-D PRE-HAART

- MOST STUDIES PRIOR TO HAART SHOWED SOME CORRELATION BETWEEN DEMENTIA AND-
  - CD4 LEVEL
  - PLASMA VIRAL LOAD
  - CSF VIRAL LOAD

VIRAL LOAD MAY ALSO HAVE PREDICTIVE VALUE
Declining incidence of HIV dementia in the Multicenter AIDS Cohort Study: This reflects the increasing use of HAART (*large arrow*) in this population of homosexual men and probably represents a best-case scenario in that other population groups, particularly, injection drug users, may be unable to achieve such good virological control, and may therefore continue to be at risk for HIV-D.
HAART TREATMENT

- GENERALLY RAPID REDUCTION IN CSF HIV RNA
  - Particularly in naïve

- BUT CSF VIROLOGICAL FAILURES FAIRLY COMMON
HAART TREATMENT

- HOWEVER
  - STILL SIGNIFICANT DEFICITS IN TREATED POPULATIONS
  - PROGRESSIVE DEFICITS REPORTED IN SOME TREATED SUBJECTS
PROGRESSION

- MOVEMENT IN BOTH DIRECTIONS

- NEAD COHORT AT JHU
  - 44% OF DEMENTED HAD PROGRESSED FROM NON-DEMENTED TO DEMENTED IN 6MTH
  - 37.5 OF DEMENTED IMPROVED TO NON-DEMENTED IN 6 MTH
Effect of HAART on cognition in Africa

Summary

- New classification incorporates milder asymptomatic phase
- Emphasis on neuropsych testing!!
- Functional assessment
Problem with diagnosis of NCI

- Research criteria available
- HIV screens unreliable, unproven
- Screening tools need neuro-battery, insensitive to milder forms
- Neuro-psych batteries: resources, specialists, time consuming
- Norms derived from well educated Caucasians
- SKILLS, EQUIPMENT
- Even with skills: no local norms, African population, tests are biased to Western constructs
Clinical Work-up for CNS Disorders in HIV Infection

- General medical work-up
- Psychiatric work-up and differential diagnosis
- Cognitive screening/neuropsych work-up
- Functional status assessment
Cognitive Screening Work-up

- Mini-Mental Status Exam
  - Insensitive
  - Higher cut offs may be useful (<26/30 should be suspect)
- HIV Dementia Scale
  - Concerns regarding reliability and validity
  - Not proven useful for MCMD
  - Cut off <10 of total 16 points
  - Gansen et al – tested in SA
- Mental Alternation test
- Executive interview
- IHDS
Cognitive-Motor Screening Work-up

- Neurological examination
  - Timed Gait
- Neuropsychological screening tests
  - Trails Making Test A & B
  - Figural Visual Scanning Task
  - California Verbal Learning Test
  - Digit-Symbol Task (WAIS-R)
**DIGIT SPAN, WMS-III**

**Name:**

**Date Administered:**

I am going to read you a list of digits, and you must repeat them back to me in exactly the same order as I gave them to you.

**Discontinue after two mistakes on one item.**

**DIGIT SPAN FORWARDS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Digit</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>123</td>
<td>123</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>456</td>
<td>456</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>789</td>
<td>789</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>ABC</td>
<td>ABC</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>DEF</td>
<td>DEF</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>GHI</td>
<td>GHI</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>JKL</td>
<td>JKL</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MNO</td>
<td>MNO</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PQR</td>
<td>PQR</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>STU</td>
<td>STU</td>
<td></td>
</tr>
</tbody>
</table>

**Total Forw. Score**

Now I am going to read you a list of digits, and you must repeat them back to me in the reverse order.

**DIGIT SPAN BACKWARDS**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Digit</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>543</td>
<td>334</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>876</td>
<td>665</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>987</td>
<td>776</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>456</td>
<td>665</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>321</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>654</td>
<td>443</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>765</td>
<td>554</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>876</td>
<td>665</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>987</td>
<td>776</td>
<td></td>
</tr>
</tbody>
</table>

**Total Back. Score**
Trail making test A

15 17 20 19 13 7 18 1 5 4 22 16 6 20 18 4 19 21 10 2 11 3 8
Trail making test B
<table>
<thead>
<tr>
<th>Age 30-50</th>
<th>Educ &lt;10yrs</th>
<th>1 SD</th>
<th>2 SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>memory</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>DSF</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>DSB</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>64</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>TMT B</td>
<td>124</td>
<td>155</td>
<td></td>
</tr>
</tbody>
</table>
Normative scores for a brief neuropsychiatric battery for the detection of HIV-associated neurocognitive deficits (HANDS) among South Africans (BMC research notes)

- Developed at McCord
- 4 neuropsych tests: DSB, DSF, TMT A, TMT B
- No special equipment, 12-15 mins
- Lay counsellors with training tested patients.

- Reference tables: age and sex.

- Implemented battery in clinic- starting ARVs irrespective of CD4.
<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>Description</th>
<th>Domains assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rey Auditory Verbal Learning</td>
<td>Recall as many words from a list of 15 words</td>
<td>memory</td>
</tr>
<tr>
<td>Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grooved peg-board</td>
<td></td>
<td>motor</td>
</tr>
<tr>
<td>Digit span forward</td>
<td>Patient is given an increasing number of random digits. They must repeat</td>
<td>Attention and</td>
</tr>
<tr>
<td></td>
<td>digits in the same order</td>
<td>concentration</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>Patient is given an increasing number of random digits. They must repeat</td>
<td>Attention, concentration and working</td>
</tr>
<tr>
<td></td>
<td>the digits in reverse order</td>
<td>memory</td>
</tr>
<tr>
<td>Trail making Test A</td>
<td>Join 25 circles with numbers in the correct sequence as quickly as possible.</td>
<td>Motor and speed of information</td>
</tr>
<tr>
<td></td>
<td>The numbers are distributed across the page and are not in order</td>
<td>processing</td>
</tr>
<tr>
<td>Trail making Test B</td>
<td>Join 25 circles with numbers and letters in alternating sequence. i.e.</td>
<td>Motor and speed of information</td>
</tr>
<tr>
<td></td>
<td>Join 1, A, 2, B, 3, C as quickly as possible</td>
<td>processing and executive function</td>
</tr>
</tbody>
</table>

Singh D.; HIV neurocognitive impairment. HIV Journal; September 2009
Functional Status Assessment (continued)

- **Assessment instruments**
  - Karnofsky Performance Scale
  - The Global Assessment of Function
  - The Social and Occupational Functioning Assessment Scale
  - The Sickness Impact Profile
  - The Direct Assessment of Functional Status
Pharmacotherapy of HIV Associated Cognitive-Motor Disorders

- Antiretroviral medications
- Immunostimulants and inflammatory mediators
- Neurotransmitter manipulation
- Nutritional interventions
WHY HAART MAY NOT STOP CNS PROGRESSION

- ARVs HAVE POOR PENETRANCE ACROSS THE BLOOD BRAIN BARRIER
- POTENTIAL FOR VIRAL SEQUESTRATION IN THE BRAIN
- MAY CAUSE CONTINUING NEUROLOGICAL DECLINE
- MAY INCREASE POTENTIAL FOR RESISTANCE WITH RESEEDING OF SYSTEMIC COMPARTMENT
CNS PENETRANCE OF ARVs

GENERALLY POOR

NRTI PENETRANCE MEDIATED BY ORGANIC ACID TRANSPORT SYSTEMS

PROTEASE INHIBITORS ELIMINATED VIA P-GLYCOPROTEINS, WHICH ARE LOCATED AT THE BBB
CSF PENETRANT ARVs

SOME STUDIES SUGGESTED IMPROVEMENT IN SOME FEATURE OF NEUROPSYCHOLOGICAL TESTING
OTHERS SHOWED NONE

THEREFORE-
MIXED RESULTS BUT INCREASING EVIDENCE PENETRANCE HAS A SIGNIFICANT EFFECT ON NEUROLOGICAL FUNCTIONING
WOULD EARLY TX PROTECT THE CNS

- PRE- HAART INCIDENCE OF DEMENTIA
  - 0.4% IN ASYMPTOMATIC STAGES
  - 16% WITH SYMPTOMATIC DISEASE

- MORE DEMENTIA WITH ADVANCING AGE
  - POSSIBLY DUE TO AGE-INDUCED LOSS OF NEURONAL RESERVE

- MCMD IS PREDICTIVE OF DEMENTIA
WOULD EARLY TX PROTECT THE CNS

- HIGH BASELINE PLASMA VIRAL LOAD PREDICTS DEMENTIA
  - CSF NOT ADEQUATELY STUDIED
- STRUCTURED TREATMENT INTERRUPTION LEADS TO ELEVATED CSF LYMPHOCYTE COUNT AND VIRAL LOAD
Classify as normal, ANI, MND or HAD

Assess all newly diagnosed HIV positive patients with Neuropsychological subtests (TMT-A, TMT-B, DSF, DSB)

Baseline investigation e.g. e.g. FBC, U & E, LFT – CT and LP (if indicated)

ANI and MND

CD4 >200

Repeat in six months. If progress to HAD start ARV

CD4 <200

Start ARVs, Monitor and reinforce adherence

CD4 >200

HAD

Treat depression and other medical conditions

Singh D.; HIV neurocognitive impairment
HIV Journal; September 2009
Clinical challenges in busy ARV clinic

- We are systematically screening people and starting HAART
- BUT
- No guidance on regimes
- What happens to people with persistent or progressive HAD
Help and contact info

- Up coming article in HIV Journal
- Reference tables: BMC research notes
- Easier tools
- ?? Accepted into ARV rollout

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