AAN 1991 Criteria: Probable HAD

1. a. Acquired abnormality in at least two cognitive (not motor) abilities
   b. Cognitive dysfunction causing impairment in work or ADLs

2. At least one of:
   a. Motor abnormality
   b. Behavioral abnormality (motivation, emotional control, social behavior)

3. Sufficient consciousness to assess cognitive abilities

4. Absence of other etiology
AAN 1991 Criteria: Probable HAD Subtypes

♦ HAD-both:
  • Criteria 1 & 2 met, with both motor and behavioral Sx

♦ HAD-motor:
  • Criterion 1 met & Criterion 2 met with only motor Sx

♦ HAD-behavioral:
  • Criterion 1 met & Criterion 2 met with only behavioral Sx
AAN 1991 Criteria: Probable MCMD

- Must have EACH of the following:

   a. Hx of at least 2 of: impaired attention/concentration; mental slowing; impaired memory; slowed movements; incoordination; personality change/irritability/lability.
   b. Acquired cognitive/motor abnormality verified by clinical exam or NP testing (# abnormal areas not specified).

2. Abnormalities from #1 cause mild impairment in work or activities of daily living.

3. Does not meet criteria for HAD or HIV-associated myelopathy.

4. No evidence of other etiology.
Some issues that emerged regarding the AAN 1991 criteria

- Degree of NP impairment is underspecified in AAN HAD and MCMD criteria
- Number of areas showing objectively documented decline underspecified in AAN MCMD criteria
- Ability to classify HAD with "mild" ADL decline has some overlap with MCMD diagnosis
HNRC Criteria for HIV neurocognitive complications: Asymptomatic Neuropsychological Impairment (ANI)

1. Performance at least 1 standard deviation below demographically corrected norms in at least 2 different cognitive areas*

2. Impairment has been present at least one month.

3. The impairment cannot be explained by comorbid conditions (e.g., substance abuse, medications, developmental disorder)†

4. The impairment does not occur solely as part of a delirium (e.g., due to CNS toxoplasmosis, lymphoma, CMV)

*At least 5 of the following 8 ability areas must be assessed: attention/information processing; language; abstraction/executive; complex perceptual motor; learning; recall/forgetting; motor skills; sensory

†If the individual with suspected ANI also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of ANI should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following termination of dependent-substance use.

HNRC Criteria for HIV neurocognitive complications: HIV-1 Associated Mild Neurocognitive Disorder (MND)

1. Acquired mild-moderate impairment in cognitive function documented by performance at least 1.0 standard deviation below demographically corrected norms in at least 2 different cognitive areas.

2. Cognitive impairment produces at least mild interference in daily functioning (report of reduced mental acuity, inefficiency at work, home, social activities).

3. Cognitive impairment has been present at least one month.

4. Cognitive impairment does not meet criteria for delirium or dementia.

5. There is no evidence of another preexisting cause for the MND†.

†If the individual with suspected MND also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following termination of dependent-substance use.

*At least 5 of the following 8 ability areas must be assessed: attention/information processing; language; abstraction/executive; complex perceptual motor; learning; recall/forgetting; motor skills; sensory
HNRC Criteria for HIV neurocognitive complications: HIV-1 Associated Dementia (HAD)

1. Acquired moderate-severe impairment in cognitive function documented by performance below 2 standard deviations below demographically corrected norms in at least 2 different cognitive areas*

2. Cognitive impairment produces marked interference in daily functioning (work, home, social activities)

3. Cognitive impairment has been present at least one month.

4. Cognitive impairment does not meet criteria for delirium or dementia.

5. There is no evidence of another preexisting cause†.

†If the individual with suspected MND also satisfies criteria for a major depressive episode or substance dependence, the diagnosis of MND should be deferred to a subsequent examination conducted at a time when the major depression has remitted or at least 1 month has elapsed following termination of dependent-substance use.

*At least 5 of the following 8 ability areas must be assessed: attention/information processing; language; abstraction/executive; complex perceptual motor; learning; recall/forgetting; motor skills; sensory
Predictive validity of AAN and HNRC criteria with autopsy confirmation of HIV encephalitis based on cases (n=39) in Cherner et al *Neurology* 2002

<table>
<thead>
<tr>
<th>AAN91</th>
<th>HNRC</th>
<th>HIVE</th>
<th>#Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAD</td>
<td>HAD</td>
<td>HIVE+</td>
<td>4</td>
</tr>
<tr>
<td>HAD</td>
<td>MND</td>
<td>HIVE+</td>
<td>9</td>
</tr>
<tr>
<td>HAD</td>
<td>NPI</td>
<td>HIVE+</td>
<td>1</td>
</tr>
<tr>
<td>MCMD</td>
<td>normal</td>
<td>HIVE+</td>
<td>1</td>
</tr>
<tr>
<td>MCMD</td>
<td>normal</td>
<td>HIVE-</td>
<td>2</td>
</tr>
<tr>
<td>normal</td>
<td>MND</td>
<td>HIVE+</td>
<td>2</td>
</tr>
<tr>
<td>normal</td>
<td>NPI</td>
<td>HIVE+</td>
<td>2</td>
</tr>
<tr>
<td>normal</td>
<td>NPI</td>
<td>HIVE-</td>
<td>1</td>
</tr>
<tr>
<td>normal</td>
<td>normal</td>
<td>HIVE+</td>
<td>8</td>
</tr>
<tr>
<td>normal</td>
<td>normal</td>
<td>HIVE-</td>
<td>9</td>
</tr>
</tbody>
</table>

Diagnostic agreement = 21/39 = 54%

Agreement on normal/abnormal dx = 31/39 = 79%

AAN dx corresponds to HIVE
HNRC dx corresponds to HIVE
Diagnostic Accuracy of AAN and HNRC Nomeclatures vis-à-vis post mortem HIVE

**Positive Predictive Power:** Number of cases with NP impairment who have HIVE

- Using AAN criteria: $15/17 = 88\%$
- Using HNRC criteria: $18/19 = 95\%$

**Misses:** Number of cases deemed NP Normal who have HIVE

- Using AAN criteria: $12/22 = 54\%$
- Using HNRC criteria: $9/20 = 45\%$

**Sensitivity:** Number of cases with HIVE who have NP impairment

- Using AAN criteria: $15/27 = 56\%$
- Using HNRC criteria: $18/27 = 67\%$

**Specificity:** Number of cases deemed NP Normal who do not have HIVE

- Using AAN criteria: $10/12 = 83\%$
- Using HNRC criteria: $11/12 = 92\%$
Three scenarios of diagnostic disagreement

1) Normal by AAN criteria and impaired by HNRC criteria
   - 3 cases: Have mild cognitive impairment but no ADL decline
   - 1 case: Has mild cognitive impairment and mild ADL decline but no self-reported complaints/ Hx of cognitive, motor, or behavioral decline

2) MCMD by AAN criteria and normal by HNRC criteria
   - 3 cases: Have normal cognitive functioning but motor or behavioral changes, along with mild ADL decline

3) HAD by AAN criteria and MND by HNRC criteria
   - 6 cases: Have mild cognitive impairment
   - 4 cases: Have mild to moderate cognitive impairment
Diagnosis of HIV neurocognitive disorders among women in Puerto Rico based on several available scales

Source: Valerie Wojna

Definitional Criteria Work Group 1: Toward an updated nosology for HIV-associated neurocognitive disorders
What is the course of neurocognitive impairment over time?

***************

Some data from HNRC, the Hawaii Aging with HIV Cohort, and NEAD
Stability of NP Impairment

Longitudinal data from HNRC

534 HIV+
141 HIV-

at least 3 visits

(total number of visits = 3722)
Proportion NP Impaired at baseline by HIV Status (HIV+ = 541; HIV- = 141)
NP Course for HIV neurocognitive states
N=534

- Stably normal: 47% (n=249)
- Stably impaired: 11% (n=60)
- Stably improved: 18% (n=95)
- Stably declined: 4% (n=24)
- Fluctuated: 19% (n=102)

All HIV+
Hawaii data: Diagnostic Transitions from Baseline to Year 1

- Nearly 1/3 (53/159) of participants who have at least some NP impairment do not meet MCMD or HAD criteria.
- Approximately 45% of these “NP abnormal” participants progress at one year.

Source: Victor Valcour
NEAD Data: Frequency of transitions among neurological states in NEAD cohort (subjects with at least 1 transition): 55% showed ≥ 1 transition

<table>
<thead>
<tr>
<th>Transition pattern</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ⇒ MCMD</td>
<td>49</td>
<td>23</td>
</tr>
<tr>
<td>Normal ⇒ HIV-D</td>
<td>10</td>
<td>4.6</td>
</tr>
<tr>
<td>MCMD ⇒ Normal</td>
<td>45</td>
<td>21</td>
</tr>
<tr>
<td>MCMD ⇒ HIV-D</td>
<td>39</td>
<td>18</td>
</tr>
<tr>
<td>HIV-D ⇒ Normal</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>HIV-D ⇒ MCMD</td>
<td>48</td>
<td>22</td>
</tr>
</tbody>
</table>

Source: Justin McArthur
Importance of demographic adjustments in interpreting neurocognitive results

Data from New York and San Diego
New York data: Diagnoses based on AAN vs. Clinical Ratings: Ethnic Disparities

Age = 44.2 (7.6)
Education = 12.2 (2.9)
Median CD4 = 191.4

Source: Desireé Byrd
Results of Using Different Normative Data Sets to Identify NP Impairment in African American Subjects

New Heaton et al 2004 norms are appropriate for use with African Americans

Source: Bob Heaton
Proportion of healthy (HIV-) Spanish-speaking subjects classified as impaired using the HRB 2004 norms vs new Spanish language norms

Source: Cherner et al., INS, Feb. 2005
Misclassification most salient at lower levels of education/literacy (Figure Learning Test)

![Bar chart showing misclassification rates by education level and language proficiency.](image)

- % Impaired
- Education levels: 0, 1-5, 6-10, 11-13, 14+
- Expected base rate

English norms vs. Spanish norms
Review of Findings

1. Current AAN criteria have good sensitivity and specificity for predicting future HIV-ence diagnosis, but positive predictive power can be enhanced by considering asymptomatic neurocognitive impairment.

2. Approximately 20% of cases with documented neurocognitive impairment do not have sufficient everyday functioning change to meet current AAN criteria.
Review of Findings

3. A substantial proportion of cases with HIV have bi-directional changes in presence or level neurocognitive impairment, and a revised nosology needs to recognize this.

4. Presence and degree of neurocognitive impairment should constitute the fundamental criterion for establishing diagnosis. Other criteria, e.g., motor disorders, emotional or personality changes, should be considered ancillary or corroborative, or criteria for defining disorder subtypes.

5. Determination of neurocognitive impairment should be based on appropriately normed tests and consider additional possible confounds.
Recommendation

Working Group 1 recommends revision of diagnostic criteria for HIV-associated neurocognitive disorders taking into account the observations above. Revised criteria should be field tested and refined accordingly before final recommendations are made.
Additional slides
AAN 1991 Criteria: Probable HAD
Resulting Diagnoses - ADL decline

† Severity of ADL decline

- **Mild:** Conspicuous decline in work performance, daily living activities, social activities, and complicated tasks, but not completely dependent. Can perform self-care.

- **Moderate:** Can’t work; needs assistance with daily living activities, self care, and walking. Can communicate basic needs.

- **Severe:** Unable to perform any activities of daily living or self-care without assistance; requires continual supervision; nearly or completely mute.
Baseline background characteristics by HIV status

<table>
<thead>
<tr>
<th>Mean (sd) or %</th>
<th>HIV+ n=534</th>
<th>HIV- n=141</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>37.1 (8.7)</td>
<td>35.6 (9.0)</td>
<td>ns</td>
</tr>
<tr>
<td>Education</td>
<td>13.5 (2.4)</td>
<td>14.2 (2.6)</td>
<td>.001</td>
</tr>
<tr>
<td>% women</td>
<td>15</td>
<td>26</td>
<td>.003</td>
</tr>
<tr>
<td>% white</td>
<td>68</td>
<td>68</td>
<td>ns</td>
</tr>
<tr>
<td>CD4 count</td>
<td>390.1 (261.0)</td>
<td>895.4 (303.4)</td>
<td>.0001</td>
</tr>
<tr>
<td>Nadir CD4</td>
<td>255.9 (233.7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Log Plasma RNA</td>
<td>4.0 (1.2)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>% HAART</td>
<td>32</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>% other ARV</td>
<td>29</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
### Baseline background characteristics by HIV status and baseline NP impairment

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>p</th>
<th>HIV-</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (sd) or %</strong></td>
<td>Impaired (n=199)</td>
<td></td>
<td>Impaired (n=20)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>38.3 (9.0)</td>
<td>.008</td>
<td>33.8 (9.33)</td>
<td></td>
</tr>
<tr>
<td>Educ</td>
<td>13.5 (2.4)</td>
<td></td>
<td>14.1 (2.2)</td>
<td></td>
</tr>
<tr>
<td>% women</td>
<td>16</td>
<td></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>% white</td>
<td>62</td>
<td></td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>CD4 count</td>
<td>373.7 (265.9)</td>
<td></td>
<td>837.9 (243.4)</td>
<td></td>
</tr>
<tr>
<td>Nadir CD4</td>
<td>224.5 (203.8)</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Log Plasma RNA</td>
<td>4.0 (1.3)</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>% HAART</td>
<td>39</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>% other ARV</td>
<td>30</td>
<td></td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Baseline background characteristics of HIV+ Ss by NP course over all available visits (minimum 3)

<table>
<thead>
<tr>
<th></th>
<th>HIV+</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (sd) or %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (sd) or %</td>
<td>Stably Normal (n=249)</td>
<td></td>
</tr>
<tr>
<td>Stably Normal (n=249)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36.3 (8.5)</td>
<td>.0004</td>
</tr>
<tr>
<td>Education</td>
<td>13.6 (2.2)</td>
<td>.08</td>
</tr>
<tr>
<td>% women</td>
<td>15</td>
<td>ns</td>
</tr>
<tr>
<td>% white</td>
<td>75</td>
<td>.06</td>
</tr>
<tr>
<td>CD4 count</td>
<td>422.1 (272.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Nadir CD4</td>
<td>287.8 (263.1)</td>
<td>ns</td>
</tr>
<tr>
<td>Log Plasma RNA</td>
<td>3.9 (1.2)</td>
<td>ns</td>
</tr>
<tr>
<td>% HAART</td>
<td>26</td>
<td>.06</td>
</tr>
<tr>
<td>% other ARV</td>
<td>28</td>
<td></td>
</tr>
</tbody>
</table>
Stability of NP status over time in 534 HIV+ and 141 HIV- Ss (minimum 3 visits)
Proportion NP Impaired Over Time by HIV Status

<table>
<thead>
<tr>
<th>Stably Impaired</th>
<th>Stably normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-</td>
<td>3</td>
</tr>
<tr>
<td>HIV+</td>
<td>11</td>
</tr>
</tbody>
</table>
NP Course by Baseline NP Status, HIV+ only

![Bar chart showing the distribution of HIV+ individuals in different NP course categories.

- Stably normal: 75%
- Stably impaired: 30%
- Stably improved: 48%
- Stably declined: 7%
- Wobbled: 22% (HIV+ Impaired), 18% (HIV+ WNL)

Definitional Criteria Work Group 1: Toward an updated nosology for HIV-associated neurocognitive disorders
Transitions in neurocognitive category between first and last visit in HIV+ HNRC participants (minimum 3 visits)