Controversies:
Screening for and Management of HAND

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Acknowledgements & Conflicts

Study Volunteers

UC San Diego
- Ronald J. Ellis
- J. Allen McCutchan
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- David Clifford
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- Ann Collier
- David Clifford

National Institutes of Health
- …Mental Health
- …Drug Abuse
- …Allergy and Infectious Diseases

Industry
- Abbvie
- ViiV
- Merck, Inc.
- Janssen
- Biogen IDEC
Should Clinicians Screen for HAND?
Should Clinicians Screen for HAND?

Neurocognitive Impairment?
Is Neurocognitive Impairment in People with HIV Disease Common and Clinically Important?
Neurocognitive Impairment is Common in Most – But Not All – Reports


19% of people with HIV in the US are taking ART and have undetectable plasma viral load.
Neurocognitive Impairment is Associated with Advanced Immune Suppression


CNS Impact of HIV is Most Evident in the Absence of Other Conditions

Advanced Immune Disease & Glial Activation

Stimulant & Opiate Use

ART Toxicity

Immune & Glial Activation

Persistent HIV Replication

Organ Disease (Liver, Vascular)

Chronic Infections

Other CNS Disorders

Aging

Neuro-cognitive impairment

Host Related

HIV Related

Drug Related
Guidelines Continue to Evolve to Favor Earlier Initiation of ART

De Cock and El-Sadr, New England Journal of Medicine, 2013; DOI: 10.1056/NEJMp1300458
CD4 Counts and Plasma Viral Loads Improve Over Time in CHARTER

Mean CD4 Count
Plasma HIV RNA ≤ 50 c/mL on ART
CSF HIV RNA ≤ 50 c/mL on ART
Many Functional Abilities Can Be Affected by Neurocognitive Impairment

**Lawton IADLs**
- Shopping and Food preparation
- Medications
- Transportation
- Financial management
- Job performance

**Other Effects**
- Traffic accidents
- Worse Survival


Symptoms and Functioning Varies Based on the Type of Assessment

Nearly a third of ANI diagnoses based on self-report were re-categorized as MND or HAD when performance-based measures were considered.

Heaton, et al. 19th CROI 2012, Abstract 77
People with ANI are at Greater Risk for Progression to More Severe HAND

ANI: n=121
NML: n=226

Relative Risk
ANI vs. NP-Normal
2.2 [CI: 1.3-3.8]

P = 0.03

Heaton, et al. 19th CROI 2012, Abstract 77
Which patients should be screened for HAND? How often should screening occur?

- **Assess all patients** with HIV disease (CEBM 5; GOR D)
  - Assessment can assist in treatment and management decisions, provide reassurance, and detect cognitive, behavioural and mood changes before symptoms arise or are acknowledged (CEBM 2b)
  - No rationale for screening only symptomatic patients (CEBM 2b)

- Assess neurocognitive functioning early in disease **using a sensitive screening tool** (CEBM 5, GOR D)

- All patients with HIV should be screened for HAND **within 6 months of diagnosis** (CEBM 5; GOR D)

- Screening should take place **before initiation of ART** (CEBM5; GOR D)
European AIDS Clinical Society Guidelines, October 2011; Available at: http://www.europeanaidsclinicalsociety.org/ [accessed 15 Nov 2011]
Which tools should be used for screening?

- No single HAND screening tool is suitable across all practice settings (CEBM 1b; GOR B)
- Choice of screening tool depends on several factors, including:
  - Availability of a neuropsychologist
  - The cost of testing and the time available for testing
  - The characteristics of the population in which it will be used (CEBM 5; GOR D)
- Where a neuropsychologist is available and suitable population norms are available, a combination of two neuropsychological tests have shown good sensitivity, including to the milder forms of HAND (CEBM 2b; GOR B)
- Repeated screening may be beneficial to detect changes over time
Which tools should be used for screening?

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- Choice of screening tool depends on several factors, including:
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  - The cost of testing and the time available for testing
  - The characteristics of the population in which it will be used (CEBM 5; GOR D)
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- Repeated screening may be beneficial to detect changes over time
<table>
<thead>
<tr>
<th>Tool</th>
<th>Benefits</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV Dementia Scale (HDS)</td>
<td>Very brief</td>
<td>Insensitive for mild HAND</td>
</tr>
<tr>
<td></td>
<td>Specific for HAD</td>
<td>Requires trained examiner</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International HDS</td>
<td>Very brief, Sensitive &amp; specific for HAD</td>
<td>Insensitive for mild HAND</td>
</tr>
<tr>
<td></td>
<td>No trained examiner</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Recall of HVLT-R</td>
<td>Very brief, Alternate forms reduce practice effect</td>
<td>Requires trained examiner</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normative data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grooved Pegboard</td>
<td>Very brief, Sensitive to motor dysfunction</td>
<td>Requires trained examiner</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normative data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Executive Interview</td>
<td>Good internal consistency</td>
<td>Less sensitive than HDS</td>
</tr>
<tr>
<td></td>
<td>Correlates w/other measures</td>
<td>Unknown accuracy in mild HAND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive functional subscale of MOS-HIV</td>
<td>Sensitive to motor dysfunction</td>
<td>Insensitive for attention or memory functioning</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief NeuroScreen</td>
<td>Brief</td>
<td>Requires trained examiner</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less sensitive for mild HAND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CogState, CANTAB</td>
<td>Automated</td>
<td>Limited validation for screening in HIV disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montreal Cognitive Assessment</td>
<td>Brief</td>
<td>Sensitivity 63%</td>
</tr>
<tr>
<td></td>
<td>Multiple languages</td>
<td></td>
</tr>
</tbody>
</table>

Screening Summary

In Favor of Screening

• Identifies people earlier in neurocognitive disease
  – May be more responsive to intervention
• Identifies treatable neuropsychiatric diseases
  – Infections e.g., syphilis
  – Substance use
  – Depression
• Enables clinics to provide needed social and medical assistance

Not In Favor of Screening

• No single tool is sensitive in all settings
• Uses clinical resources, which are limited
  – Resources to confirm screening findings may not available
• Increases anxiety
  – Only 25% of ANI patients progress over 3 years
  – No proven treatments
• Leads to interventions that could worsen disease
If you do not have the resources to complete the diagnosis of HAND, should you screen?
Management of HAND
If the Effects of ART Drugs Differ in the CNS, Can We Translate this into Clinical Practice?
Estimates of higher drug distribution into the CNS are associated with:

- Lower HIV RNA levels in CSF
- Lower soluble biomarker levels in CSF
- Lower frequency of neurocognitive impairment in some but not all analyses

<table>
<thead>
<tr>
<th></th>
<th>50 c/mL Assay</th>
<th>2 c/mL Assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional</td>
<td>Yes(^1)</td>
<td>Yes(^3)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>Yes(^2)</td>
<td>No(^4)</td>
</tr>
<tr>
<td>Comment</td>
<td>Included patients with plasma HIV RNA &gt; 50</td>
<td>HIV RNA 2-50 c/mL associated with NCI</td>
</tr>
</tbody>
</table>

Letendre et al, \(^1\) CROI 2010, \(^2\) CROI 2012, \(^3\) CROI 2009, \(^4\) CROI 2013
Higher CPE Values Correlate with Undetectable HIV RNA in CSF Over Time

2,207 CSF Viral Loads in 413 Volunteers in CHARTER

Letendre et al, 19th CROI, 2012, Abstract 473
In CHARTER, CPE Values Correlate with Other Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direction (Higher CPE)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV RNA in CSF*</td>
<td>Lower</td>
<td>$\chi^2 = 10.8$</td>
</tr>
<tr>
<td>Number of ART drugs</td>
<td>More</td>
<td>r = .71</td>
</tr>
<tr>
<td>Age</td>
<td>Older</td>
<td>r = .12</td>
</tr>
<tr>
<td>Duration of Regimen</td>
<td>Longer</td>
<td>r = .13</td>
</tr>
<tr>
<td>VACS Values</td>
<td>Higher</td>
<td>r = .10</td>
</tr>
<tr>
<td>Duration of HIV</td>
<td>Longer</td>
<td>r = .05</td>
</tr>
</tbody>
</table>

- **Not**: HCV serostatus, Neuropsychiatric comorbidities, ethnicity, gender, AIDS, nadir or current CD4

* Association with HIV RNA in CSF remains statistically significant in multivariable regression models that include these covariates
Higher CPE Values Correlate with Lower IP-10, sCD14, and Neopterin in CSF During HIV Suppression

<table>
<thead>
<tr>
<th>CSF Biomarker</th>
<th>All on ART</th>
<th>HIV RNA Plasma ≤ 50</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>r</td>
<td>p value</td>
</tr>
<tr>
<td>SDF-1α</td>
<td>144</td>
<td>-0.26</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>IP-10</td>
<td>255</td>
<td>-0.18</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>sTNFR-II</td>
<td>87</td>
<td>-0.30</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>IL-6</td>
<td>256</td>
<td>-0.12</td>
<td><strong>0.05</strong></td>
</tr>
<tr>
<td>Neopterin</td>
<td>45</td>
<td>-0.29</td>
<td><strong>0.056</strong></td>
</tr>
<tr>
<td>TNF-α</td>
<td>256</td>
<td>-0.12</td>
<td><strong>0.058</strong></td>
</tr>
<tr>
<td>MCP-1</td>
<td>283</td>
<td>-0.06</td>
<td>0.28</td>
</tr>
<tr>
<td>sCD14</td>
<td>59</td>
<td>-0.02</td>
<td>0.88</td>
</tr>
</tbody>
</table>
### ART Characteristics Are Also Associated with CSF Viral Escape

<table>
<thead>
<tr>
<th>First Author</th>
<th>Sample Size</th>
<th>% with CVE</th>
<th>ART Correlates</th>
<th>CSF Correlates</th>
<th>Other Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rawson (2012)</td>
<td>142</td>
<td>21%</td>
<td>↓ CPE</td>
<td></td>
<td>↑ Plasma HIV RNA ↓ Age</td>
</tr>
<tr>
<td>Cusini (2012)</td>
<td>60</td>
<td>6.7%</td>
<td>↓ CPE</td>
<td>↑ Protein</td>
<td>↑ Peak Plasma HIV RNA, ↑ Age</td>
</tr>
<tr>
<td>Eden (2010)</td>
<td>69</td>
<td>11%</td>
<td>Absence of ZDV</td>
<td>↑ Neopterin</td>
<td></td>
</tr>
<tr>
<td>Perez-Valero (2012)</td>
<td>1,264</td>
<td>4.4%</td>
<td>PI/r Use, ATV Use</td>
<td>↑ WBCs</td>
<td>↑ Duration of HIV ↑ Platelets ↑ Serum Protein</td>
</tr>
<tr>
<td>Weighted Median (IQR)</td>
<td>8.8% (5.0%-18.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Two published case series also supported a role for ART characteristics in CVE; Canestri et al, CID 2010; Peluso et al, AIDS 2012
How Well Do These Findings Translate to Cognition?

**Important considerations:**

1. Susceptibility to neurocognitive impairment varies between patients
   - Balance between ART safety and effectiveness likely differs between patients

2. Not all neurocognitive impairment is due to HIV
   - ART would not benefit NCI due to non-HIV causes

3. Pathogenesis of ANI, MND, and HAD may differ
   - The 3 conditions may not respond similarly to ART
ART Affects an Early Step in HAND Pathogenesis... Later Steps May Not Respond As Well
Published Reports with Higher Quality Methods Found Associations with CPE

- Cysique et al, 2004, N = 97
- Chang et al, 2003, N = 33
- Cysique et al, 2009, N = 31
- Tozzi et al, 2009, N = 185
- Letendre et al, 2008, N = 467
- Smurzynski et al, 2011, N = 2,636

Effect Size

Cysique et al, BMC Neurology, 2011;11:148
## CPE-Related Reports in 2013

<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>N</th>
<th>NP</th>
<th>Duration</th>
<th>Finding</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciccarelli</td>
<td>C-S</td>
<td>101</td>
<td>C</td>
<td>-</td>
<td>↑ CPE associated with better functioning</td>
<td>2010 version stronger than 2008 version</td>
</tr>
<tr>
<td>Rourke</td>
<td>C-S</td>
<td>417</td>
<td>C</td>
<td>-</td>
<td>↑ CPE associated with better functioning</td>
<td></td>
</tr>
<tr>
<td>Fabbiani</td>
<td>C-S</td>
<td>215</td>
<td>C</td>
<td>-</td>
<td>Adjusted CPE associated with better functioning</td>
<td>Adjusted CPE using GSS</td>
</tr>
<tr>
<td>Vassallo</td>
<td>L</td>
<td>96</td>
<td>C</td>
<td>22 months</td>
<td>↑ CPE associated with better functioning</td>
<td></td>
</tr>
<tr>
<td>Ellis</td>
<td>RCT</td>
<td>49</td>
<td>C</td>
<td>16 weeks</td>
<td>No overall statistically significant benefit; Benefit in subgroup</td>
<td>Planned enrollment 120</td>
</tr>
<tr>
<td>Kahouadji</td>
<td>C-S</td>
<td>93</td>
<td>B</td>
<td>-</td>
<td>↑ CPE associated with worse FAB scores</td>
<td>Substantial methodologic flaws</td>
</tr>
</tbody>
</table>

C-S = Cross-sectional, L = Longitudinal, RCT = Randomized clinical trial, C = Comprehensive, B = Brief

Recent Reports
Cognitive Intervention Trial 2

• Multicenter, NIH-funded clinical trial randomizing people with HAND to initiating or changing to either CNS-targeted or untargeted ART

• **Primary endpoint:** 16 weeks of ART

• Adaptive randomization to balance:
  – ART experience (naive vs. experienced)
  – Entry CD4+ T-cell count (<200 vs. ≥200)
  – Severity of impairment (mild vs. moderate-severe)
  – HCV serostatus

*Ellis et al, 20th CROI, 2013, Abstract 20*
Enrollment and Disposition

Planned Enrollment: 120

- CNS-T: n = 29
  - ITT Analysis: n = 26
    - AT Analysis: n = 23
    - 3 Protocol Violations
  - 3 Lost to Follow-Up

- Non-CNS-T: n = 30
  - ITT Analysis: n = 23
    - AT Analysis: n = 19
    - 4 Protocol Violations
  - 7 Lost to Follow-Up

ITT = Intent-to-treat
AT = As treated

Ellis et al, 20th CROI, 2013, Abstract 20
Potentially Influential Differences Occurred Between Arms at Baseline

<table>
<thead>
<tr>
<th></th>
<th>CNS-T</th>
<th>Non-CNS-T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV Naive</td>
<td>12 (35%)</td>
<td>13 (26%)</td>
<td>&gt; 0.20</td>
</tr>
<tr>
<td>Plasma VL (&lt; 50 c/mL)</td>
<td>7 (27%)</td>
<td>6 (26%)</td>
<td>&gt; 0.20</td>
</tr>
<tr>
<td>Entry CD4</td>
<td>214 [5, 964]</td>
<td>306 [3, 1224]</td>
<td>&gt; 0.20</td>
</tr>
<tr>
<td>Nadir CD4 &lt; 200</td>
<td>16 (67%)</td>
<td>8 (38%)</td>
<td>0.08</td>
</tr>
<tr>
<td>HCV seropositivity</td>
<td>9 (35%)</td>
<td>3 (13%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Randomized Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number ARVs</td>
<td>4</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>Relative PSS</td>
<td>1</td>
<td>0.95</td>
<td>0.19</td>
</tr>
<tr>
<td>ARVs most different between arms</td>
<td>NVP, LPV/r, ZDV, ABV, FTC</td>
<td>ETR, DRV/r, TDF, 3TC</td>
<td>--</td>
</tr>
</tbody>
</table>

Ellis et al, 20th CROI, 2013, Abstract 20
The Primary Outcome Did Not Differ At Week 16

<table>
<thead>
<tr>
<th></th>
<th>CNS-T (N = 26)</th>
<th>Non-CNS-T (N = 23)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted GDS change</td>
<td>-0.14 (0.54)</td>
<td>-0.07 (0.43)</td>
<td>&gt; 0.20</td>
</tr>
<tr>
<td>(mean, SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma VL &lt; 50 c/mL (%)</td>
<td>54%</td>
<td>82%</td>
<td>0.06</td>
</tr>
<tr>
<td>CSF VL &lt; 50 c/mL (%)</td>
<td>68%</td>
<td>87%</td>
<td>0.17</td>
</tr>
<tr>
<td>Change in CD4+ T-cells</td>
<td>+41 (104)</td>
<td>+55 (154)</td>
<td>0.33</td>
</tr>
<tr>
<td>(mean, SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ellis et al, 20\textsuperscript{th} CROI, 2013, Abstract 20
In a Planned Secondary Analysis, Those Who Enrolled with Suppressed HIV RNA May Have Benefitted from CNS-T ART

**Global Deficit Score Change (Baseline to Week 16)**

- **CNS-T (n = 19)**
- **Non-CNS-T (n = 17)**
- **CNS-T (n = 7)**
- **Non-CNS-T (n = 6)**

Plasma HIV RNA > 50 c/mL

Plasma HIV RNA ≤ 50 c/mL

**Standardized Effect Size = 1.1**
ART Use Continues to Evolve

N(t)RTIs

Proportion

Year

2003 2004 2005 2006 2007 2008 2009 2010 2011

TDF

ABC

ZDV

PLs

Proportion

Year

2003 2004 2005 2006 2007 2008 2009 2010 2011

ATV

LPV

DRV

NNRTIs and RTG

Proportion

Year

2003 2004 2005 2006 2007 2008 2009 2010 2011

EFV

RTG

NVP

CHARTER
Unpublished Data
Several Other Characteristics May Influence Neurocognitive Functioning

Monocyte Efficacy

Neuronal Toxicity

HCV Co-infection

Shikuma et al, Antiviral Therapy 2012, 17: 1233-42

Robertson et al, J Neurovirol 2012, 18: 388-299

Letendre et al, 20th CROI, 2013, Abstract 407
Mind Exchange Guidance Regarding ART

• No evidence supports initiation of therapy with better CNS-penetrating regimens in neurocognitively normal patients (CEBM 5; GOR D)

• In the treatment of existing neurocognitive impairment, better neurocognitive performance has generally been observed in patients receiving higher CPE cART regimens (CEBM 2b)
  – Evidence base is limited and some of the data are contradictory regarding the potential benefits of CPE cART (CEBM 2b)

Kenneth H. Mayer, Section Editor

The Mind Exchange Working Group
Even if Some Drugs Are More Safe and Effective in the CNS than Others, Treatment Decisions Should Not be Made Without Considering Other Conditions Affecting the Patient
When Treating the CNS, Focus First on Conditions that Have Well Defined Treatments
Cognitive Rehabilitation for HAND

HIV-associated neurocognitive deficits can be improved using cognitive rehabilitation techniques such as self-generation, cueing, and strategic visualization/imagery.

Summary & Conclusions

• Neurocognitive impairment is common in people with HIV but not all neurocognitive impairment is due to HIV disease
• Screening tools for neurocognitive impairment are available but confirmatory assessments are not available in all clinics
  – Self-report of symptoms alone may underestimate prevalence
  – Do not change ART based solely on screening results
  – Diagnose and treat what you can
• ART that has better CNS distribution might better treat neurocognitive impairment due to HIV disease
  – Supportive observational and non-randomized interventional data
  – Inconclusive randomized clinical trial: Benefit may be greatest in people who have already achieved viral suppression
  – In addition to drug distribution, neurotoxicity and monocyte activity may be important to consider
Summary & Conclusions

• Further strengthen efforts to...
  – Identify people earlier in disease (reduce late presenters)
  – Initiate therapy earlier in disease

• Clinical management of CNS complications of HIV disease requires a multifaceted approach
  – More guidance is available to assist clinicians than in the past
  – Test and treat...for neurocognitive impairment
  – Provide social and medical support
  – Monitor for worsening disease
Cognitive Neurorehabilitation of HIV-associated Neurocognitive Disorders: A Qualitative Review and Call to Action

Erica Weber • Kaitlin Blackstone • Steven Paul Woods

HIV-related Neuropathology
- Synapto-dendritic Injury
- Vasculopathy
- Gliosis
- HIV encephalitis

Neural Systems Affected
- Frontostriatal
- Temporolimbic

Neurocognitive Impairments
- Executive Functions
- Attention/WM
- Psychomotor Speed
- Episodic Memory

Everyday Functioning Declines
- ART Non-adherence
- Vocational Problems
- IADL Dependence

Poor Health Outcomes
- Immunovirologic
- HIV-related Morbidity
- HIV-related Mortality

Prophylactic Approaches
- Early ART Initiation
- Early Behavioral Stimulation (e.g., diet, exercise)
- Early Cognitive Stimulation (e.g., promote brain reserve)

Restorative
- ART Treatment
- Non-ART Treatment
- Cognitive Stimulation
- Behavioral Stimulation

Compensatory
- Utilize Automatic Cognitive Processes
- Support Deficient Strategic Processes
- Habitual Behaviors

Approaches to Rehabilitation
• When you’re a hammer, everything looks like a nail...
• But sometimes a nail is a nail
Choosing Not to Screen for Neurocognitive Impairment is Like Throwing the Baby Out With the Bathwater

Reasons to screen for neurocognitive impairment

• HAND is clinically important
• Screening does not require substantial resources
• No randomized trial has demonstrated a safe and effective therapy for HAND

The Mind Exchange Working Group

Many practical clinical questions regarding the management of human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND) remain unanswered. We sought to identify and develop practical answers to key clinical questions in HAND management. Sixty-six specialists from 30 countries provided input into the program, which was overseen by a steering committee. Fourteen questions were rated as being of greatest clinical importance. Answers were drafted by an expert group based on a comprehensive literature review. Sixty-three experts convened to determine consensus and level of evidence for the answers. Consensus was reached on all answers. For instance, good practice suggests that all HIV patients should be screened for HAND early in disease using standardized tools. Follow-up frequency depends on whether HAND is already present or whether clinical data suggest risk for developing HAND. Worsening neurocognitive impairment may trigger consideration of antiretroviral modification when other causes have been excluded. The Mind Exchange program provides practical guidance in the diagnosis, monitoring, and treatment of HAND.

Keywords. AIDS dementia complex; HIV-associated dementia (HAD); HIV-associated neurocognitive disorder (HAND); HIV encephalopathy; neurocognitive impairment.
Not all people with HIV will develop NCI.

CHARTER Baseline Data
Do the Benefits of Screening for Neurocognitive Impairment in People with HIV Outweigh the Risks?
• Argument: You should not screen for MND because you might find ANI
  – This is akin to saying, “Don’t investigate chest pain because sometimes it’s not due to coronary disease”

• Argument: Telling people that they have ANI is dangerous and unethical
  – This is akin to saying, “Telling people that their chest pain is due to esophageal spasm is dangerous and unethical”
Neurocognitive Impairment is Common in Most But Not All Reported Cohorts

Goals of Mind Exchange program

• Identify and address the most important clinical questions relating to the management of HAND
• Use robust methods to reach expert consensus on current best practice in screening, diagnosis, monitoring, treatment and prevention of HAND
• Facilitate maximum exchange of the outputs of the programme, to ensure that best practice in managing CNS issues related to HIV, specifically HAND, is understood and implemented in the HIV community
• Identify areas that may require additional research
<table>
<thead>
<tr>
<th>Level</th>
<th>Therapy/Prevention, Aetiology/Harm</th>
<th>Prognosis</th>
<th>Diagnosis</th>
<th>Differential diag/symptom prevalence</th>
<th>Economic and decision analyses</th>
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<tr>
<td><strong>Level 1A</strong></td>
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<td>1a SR (with homogeneity*) of RCTs</td>
<td>SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations</td>
<td>SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres</td>
<td>SR (with homogeneity*) of prospective cohort studies</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
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<td><strong>Level 1B</strong></td>
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<td>Individual RCT (with narrow Confidence Interval)</td>
<td>Individual inception cohort study with &gt; 80% follow-up; CDR† validated in single population</td>
<td>Validating** cohort study with good††† reference standards or CDR† tested within one clinical centre</td>
<td>Prospective cohort study with good follow-up***</td>
<td>Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence, and including multi-way sensitivity analyses</td>
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<td>SR (with homogeneity*) of case-control studies</td>
<td>SR (with homogeneity*) of 1b and better studies</td>
<td>SR (with homogeneity*) of 1b and better studies</td>
<td>SR (with homogeneity*) of Level 1 economic studies</td>
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<td>Individual Case-Control Study</td>
<td>Non-consecutive study, or without consistently applied reference standards</td>
<td>Non-consecutive cohort study, or very limited population</td>
<td>Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations,</td>
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<td><strong>Level 4</strong></td>
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<td>Case-series (and poor quality cohort and case control studies§§)</td>
<td>Case-series (and poor quality prognostic cohort studies***))</td>
<td>Case-control study, poor or nonindependent reference standard</td>
<td>Case-series or superseded reference standards</td>
<td>Analysis with no sensitivity analyses</td>
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[Link to CEbm](http://www.cebm.net/index.aspx?o=1025)
## Grades of recommendation

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<tr>
<td>A</td>
<td>Consistent level 1 studies</td>
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<tr>
<td>B</td>
<td>Consistent level 2 or 3 studies or extrapolations from level 1 studies</td>
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<tr>
<td>C</td>
<td>Level 4 studies or extrapolations from level 2 or 3 studies</td>
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<td>D</td>
<td>Level 5 evidence or troublingly inconsistent or inconclusive studies of any level</td>
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When should CSF analysis be performed in the management of HAND?

-Paola Cinque & Jacques Gasnault

- CSF analysis should be performed in patients who have neurological symptoms or signs, ideally at the first presentation (CEBM 2a; GOR B)

- In untreated patients, CSF analysis would be better performed just before initiation of ART. In treated patients, CSF analysis would be better performed just before a change in ART (CEBM 2b; GOR C)

- Since almost all patients will have clearance of HIV RNA in CSF during ART, there is no general indication to repeat CSF analysis during follow-up (CEBM 2b; GOR B)
  - Possible exceptions include patients whose ART was changed for CSF viral escape or who do not neurologically improve
What interventions should be considered in treated patients with persistent or worsening HAND and CSF viral load <50 copies/mL?

-Daniel Podzamczer & Christian Eggers

- **Consider other causes** of NCI, such as non-infectious types of dementia (e.g., vascular dementia), major depressive disorder, current drug use, and infections (CEMB 5; GOR D)
  - Diagnostic measures may include brain MRI, lumbar puncture and psychiatric evaluation
- Identify whether HIV RNA are detectable or undetectable
- **If HIV RNA is detectable in plasma** but not CSF, *adapt the regimen* according to resistance profiles and possibly the CPE score (CEBM 2b; GOR C)
- **If HIV RNA is undetectable in plasma and CSF**, the same considerations apply but the evidence is less strong (CEBM 2c; GOR C)

*Clinical Infectious Diseases Submission Submitted June 2012*
What is the nature of the legacy effect?

- Neuroadaptation
- Dysregulated immune and glial responses
Interim Summary

• ART characteristics are associated with surrogate markers of HIV disease in the CNS
  – HIV RNA levels in CSF
  – Biomarkers of immune/glial activation in CSF

• Associations are present in people taking suppressive ART

• ART characteristics are also associated with CSF viral escape
  – The clinical significance of CVE is unknown
How Can We Correctly Translate These Findings to Clinical Practice?

1. ART portfolio and practice continues to grow and diversify
   - More potent and less toxic drugs are increasingly used
   - CNS benefits of HIV suppression and immune recovery alone are likely substantial
   - How does toxicity outside the CNS affect the CNS?

2. Treatment guidelines change more quickly than the field can perform CNS clinical trials
   - Patients are starting ART at higher CD4+ T-cell counts

3. Surrogate biomarkers are critically important in making clinical trials of ART cost-effective
   - Unmet need in CNS clinical trials
Interim Summary

• Analyses with larger sample sizes and more thorough assessments typically found beneficial associations between estimated drug distribution and neurocognitive functioning.

• Improving estimated drug distribution into the CNS might be most beneficial in impaired patients who are already taking suppressive ART:
  – InMIND clinical trial in the ACTG (A5324)

• Factors other than drug distribution may influence the relationship with neurocognitive functioning:
  – CPE values are based largely on CSF drug concentrations, which may not reflect concentrations in brain tissue.